EARLY DETECTION OF COPD IN ASYMPTOMATIC SMOKERS USING SPIROMETRY

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CERTIFICATE

This is to certify that the dissertation entitled “EARLY DETECTION OF COPD IN ASYMPTOMATIC SMOKERS USING SPIROMETRY is a bonafide original work of Dr. T. MOHANASUNDARAM in partial fulfillment of the requirements of M.D General Medicine [Branch- 1] examination of THE TAMILNADU Dr. M. G. R. MEDICAL UNIVERSITY to be held in April 2015.

Prof. Dr. P. KANAGARAJ, M.D.,
HOD & UNIT-I CHIEF
Department of Medicine
K.A.P.V. Govt. Medical College
M.G.M. Govt. Hospital,
Tiruchirappalli.

Prof. Dr. P. KARKUZHALI, M.D.,
DEAN
K.A.P.V Govt. Medical College
M.G.M.Govt. Hospital,
Tiruchirappalli.
DECLARATION

I Solemnly declare that the dissertation titled “EARLY DETECTION OF COPD IN ASYMPTOMATIC SMOKERS USING SPIROMETRY” is done by me at K.A.P.VISWANATHAM GOVT MEDICAL COLLEGE, TIRUCHIRAPPALLI under the guidance and supervision of Prof. Dr. P.KANAGARAJ. M.D., This dissertation is submitted to The Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfillment of requirements for the award of M.D Degree [Branch-1] in General Medicine

Place: Tiruchirappalli
Date: Dr.T.MOHANASUNDARAM
Post Graduate Student
M.D. General Medicine
K.A.P.V Government Medical college & M.G.M.Govt. Hospital,
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ABSTRACT

KEY WORDS – EARLY DETECTION,COPD,ASYMPTOMATIC SMOKERS,PFT

AIM OF THE STUDY:

Smokers with suspected COPD seek medical attention when they become dyspnoic on mild to moderate exertion, but by than half of the ventilator reserves are lost irreversibly. Hence it seems logical to diagnose COPD early before development of significant symptoms. Since smoking cessation in COPD is found to reduce rapid decline of ventilator function in smokers and to make an attempt to quit smoking in south Indian population

MATERIALS AND METHODS:

Patients attending outpatient department at MGM Govt. Hospital attached to KAPV Govt. Medical College, Tiruchirappalli

EASY ONE spirometer

TYPE OF STUDY:

Unicentric Prospective description study.

USEFULNESS OF THE STUDY:

Chronic obstructive pulmonary disease (COPD) is a major case of chronic morbidity and mortality. Third leading cause of death in 2020. Smoking cessation will improve quality of life and decrease the morbidity and mortality.
INTRODUCTION

Among Non communicable diseases COPD is emerging as one of the leading cause of mortality in INDIA. The incidence and prevalence of COPD is increasing throughout the world with more population is reaching the age group, above 60 years at which the disease normally develops.

COPD is now ranked sixth among the leading cause of death worldwide according to 1990 world burden of disease study. It is also projected to become third leading cause of mortality by 2020.¹

Prevalence of COPD in people aged more than 30 years in India is 2.7% in females and 5% in males according to meta analysis of population based study by Jindal SK et al.²

Smoking not only causes health hazard to individual also produces environmental tobacco smoking (ETS) to non smokers as it contaminates the atmosphere

Among various causes of COPD tobacco smoking is leading cause. Smokers often ignore the early symptoms of COPD such as cough and sputum production. Even treating physician often ignores it as normal in smokers.
Smokers seek physicians attention only when they develop mild to moderate exertional dyspnoea by the time 50% of their ventilatory reserves lost. The loss is also irreversible.\(^3\)

Therefore it is necessary to diagnose COPD incidence earlier in smokers. So that measures such as smoking cessation can be initiated at appropriate time and preserve the ventilatory capacity in smokers.\(^4\)

Post bronchodilator Spirometry remains the gold standard for diagnosis and follow up of COPD patients.\(^5\)

Air flow limitation is the hallmark of COPD. It is most objectively measured and reproduced by spirometry.

Spirometry is best standardized and according to GOLD criteria it can categorize the severity of disease.

This study is done to detect COPD earlier in south Indian smokers and to analyze the association of age of onset, duration, pack years, smoking index and severity of disease according to GOLD criteria.
REVIEW OF LITERATURE
REVIEW OF LITERATURE

Smoking cessation dates back to 1975 when Norwegian tobacco act banned all forms of advertisements.\textsuperscript{6}

The relationship between cigarette smoking and decline in lung function was studied by Fletcher and Peto et al in 1977 and the same was published in British medical journal in 1977 as the natural history of chronic airflow obstruction. They published the graphical representation of smoking and smoking cessation and effects on lung function.\textsuperscript{7}

The earlier 1977 Fletcher and Peto curve demonstrated slower decline in lung function during early stages. The curve still holds landmark in understanding the natural history of COPD.

Screening for Early detection of COPD among smokers started in Finland in 1998 through program for chronic bronchitis and COPD. In this program early detection of COPD using spirometry was done and patients were followed by smoking cessation clinics.\textsuperscript{8}

In Swedes study, 40 to 55-year-old inhabitants who smoked and symptomatic or non symptomatic COPD were invited to participate in the study. The participants were given placards and subjected to have spirometry. Of the approximately 5332 eligible smokers in that area, only 512 (9.6\%) responded. Out of which 73\% had a normal spirometry and
27% had COPD. In this study only 40-55 years age group included. They also included already existing COPD patients. 43% males and 57% females participated in this study but female smokers are low in our country like India. 6 out of 147 participants had asthma during the study. Bronchial asthma patients are not excluded from study. Stralelis G, et al designed this study to assess a method to detect COPD at an early stage.  

Kohansal, Martinez-Camblor, Agusti, et al. done The Framingham Offspring cohort which was started between 1971 and 1975 includes 5,124 males and females all of which had reliable spirometric measurements and appropriate clinical information according to internal National Heart, Lung, and Blood Institute–National Institutes of Health standards smoking increases the rate of reduction of FEV1 in both males and female. They also established that there is considerable variability in the rate of decline of pulmonary function in constant smokers, both in males (from 8 to 63 ml/yr) and females (from 14 to 49 ml/yr). However, this is the first time that a huge cohort of both males and females, with a extensive age range, is followed for up to 26 years to depict pulmonary function changes from adolescence to Old age in healthy never-smokers and to investigate the effects of smoking and smoking cessation. the results were published in American journal of respiratory and critical care medicine vol 180 2009. Limitations of this study are only four spirometry
values available for each participant and several confounders like occupational exposure and environmental tobacco smoke were not excluded.\textsuperscript{10}

Gorecka, et al from Poland demonstrated that diagnosis of Airflow limitation shared with smoking cessation advice increased smoking cessation rate. High risk population screening for COPD have been investigated and implemented in Poland in this study out of 11027 smokers more than 40 years screened for airflow obstruction was found in 24.3\% of smokers.\textsuperscript{4}

In Lung health study (LHS), a large multi-centric study conducted in USA and Canada, spirometry screening of more than 73,000 smokers aged 35 to 60 years was performed in 10 centers. Air flow limitation was noted in 21.8\% to 35.7\% (mean 25\%) cases and severe obstruction (FEV1 <50\% of predicted) was seen in 5\% of total cases. In LHS study symptomatic smokers were also included. Hence prevalence was high in that group.\textsuperscript{11}

Zielinski et al performed a study called “Know the age of your lung study group” evaluated the usefulness of mass spirometry in detection of airflow limitation in high risk smoking population above 39 years of age. Outof 11027 subjects were screened with mean age of 51.8 ± 12.5 years. The average smoking history of 26.1 ± 16.8 pack-years (equal to smoking index of 522±336). In general obstruction was noted in 24.3\% cases.
Mild obstruction was seen in 9.5%, moderate in 9.6% and severe in 5.2% subjects. Analysis of sub-groups in the study threw light that obstruction seen in 30.6% of smokers above 40 years of age. This correlate with smoking history of more than 10 pack years (equivalent to smoking index 200). In contrary only 8.3% of smokers below 40 years and having smoking history of less than 10 pack years (equivalent to smoking index 200).12

P.L. Enright, M. Studnicka, J. Zielinski, from The University of Arizona, Tucson, USA conducted study using handy or office spirometer along with primary care physicians for early detection of COPD in smokers. They have demonstrated that recent spirometers are weightless, less space occupying, easy to handle and can be used by primary care physicians. Spirometry to detect and manage COPD and asthma in the primary care setting study also done according to GOLD criteria. FEV1/FVC or FEV1/FEV6 ratio is taken as reference for airflow obstruction detection. So our study we utilized microprocessor enabled spirometer. Microprocessor enabled spirometer can be connected to computer to analyze the data as done in the above study.13

In North India Barthwal MS, and Singh S studied the occurrence of COPD in high risk population in Military institutions in Pune, Maharashtra using office spirometry. They have analyzed 460 patients and found air flow obstruction in 12.6% of smokers. The sample size for this study has
been calculated based on the data available from foreign authors. They also pointed out that prevalence of COPD increases as age advance. In this study they used 40 years as age cut off. With the available data from India we planned to conduct the study in South Indian population. In our study sample size was calculated based on this study. So prevalence of 12.6% has been used to calculate sample size.\textsuperscript{14}

In DIDASCO study which was designed to analyze diagnostic criteria for COPD and asthma. They have divided the patients into two groups. One group was screened with spirometry after inhaled steroids and another with beta agonist.

They screened patient between 35-70 years. GOLD criteria was used to categorize the patients for airflow obstruction. Patients were analyzed for airflow reversibility of 12% from pre to post 400 mcg inhaled salbutamol in FEV1. Patients with reversible airflow limitations were diagnosed as asthma. This study clearly demonstrated that spirometry can be used to detect obstructive lung disease in general practitioner's office using FEV1/FVC ratio as reference value. This study also thrown light that 42% of patients with obstructive disease could not have been diagnosed without spirometry. Thus they recommended routine use of spirometry for obstructive lung disease diagnosis and follow up.\textsuperscript{15}
In India Moorthy and Sastry published the report called burden of diseases in India. In that report on the economic burden of COPD in our country pointed out that prevalence of obstructive lung disease is high compared to north India. Prevalence in Madras (Chennai) is 10.2%. So it is rationale to have sample size of around 12% prevalence for our study. That comes roughly 160-170 subjects.\(^1\)

**SMOKING INDEX:**

In countries like India smoking of tobacco varies between individuals. It may be either cigarette or bidis. Quantity or number also differs.

Cigarettes are 10 per pack and bidis 15-24 per pack. So quantum of smoking by pack years is not applicable to our country. Thus evolved smoking index. Which is expressed as number of cigarettes/bidis smoked per day multiplied by years of smoking. It is not the amount of tobacco present per bidi or cigarette but total particulate matter (TPM) matters when degree of exposure is concerned. TPM per bidi is 23-30 mg which is equal to nicotine content of 1.72-2.05 mg. in cigarette TPM is 21.16-21.94 mg and nicotine content is 1.04-1.21 mg. mean while as we compare pack year and smoking index for example 1 bidi per day for 10 years is same as 10 bidis / day for 1 year. It clearly indicates the amount of exposure.
SI is also categorized as mild 100, moderate 100-300 and severe 300 from Lung India, smoking index- a measure to quantify cumulative smoking exposure, 1988.17

With all these literature review the original curve of Fletcher and Peto has been modified and published as follows in natural history of obstructive lung disease. The earlier curve predicted that lung damage occurs at old age but it was proved wrong. The newer concept is damage to lung volumes in smokers occur at much early as predicted by spirometry.

![Modified Fletcher-Peto curve]

Modified Fletcher-Peto curve redrawn by Jones & Østrem to incorporate findings of recent advances in the natural history of COPD including FEV1 decline data from the UPLIFT study demonstrating greater annual rate of FEV1 decline during early stages of disease.
This modified curve of Fletcher and Peto clearly shows that smoking cessation started at earlier age is more beneficial than at later age in regard to obstructive lung pathology. The curve also gives clear evidence that smoking cessation started before forty years is more beneficial than later. So we included from age 25 years in this study. Any intervention that is done after half of lung volume is lost is not useful for improving the quality of life in COPD patients. So our aim is to identify the smokers at risk in earlier stage so that they can be motivated for smoking cessation.
TOBACCO SMOKING

Half of all regular cigarette smokers will eventually be killed by their habit.18. Death due to tobacco is one million in developing countries. This will increase to 10 million in 2020.19

Smoking causes increase in incidence of death due to carcinoma lungs, respiratory tract carcinoma, COPD and corpulmonale.

It also advances the incidence of coronary artery disease and cerebrovascular disease related death.

Smoking cessation decreases the morbidity and mortality related to disease of tobacco.

Smoking habit starts for psychosocial reasons like parental smoking, peer stress, feel of independence, rebelliousness usually during adolescence.20

Once started pharmacological aspects of nicotine makes it as habit which causes psychological advantages in mood of an individual and causes the habit to persist.
Russell described smoking as “probably the most addictive and dependence producing form of object specific self gratification known to man”.\textsuperscript{21}

In developing countries the pattern of smoking is different from developed world. 50\% of men and only 10\% females smoke in developing countries. Asia is accounting for about 50\% of world’s cigarette smoke.

\textbf{SAFE CIGARETTES !!}

\textbf{NO CIGARETTE IS SAFE} including substitutes like synthetic tobacco, glycerol particles and modified cellulose.\textsuperscript{22}
HEALTH EFFECTS OF SMOKING

RESPIRATORY SYSTEM:

COPD, carcinoma of lungs, carcinoma of upper respiratory tract particularly laryngeal carcinoma.\textsuperscript{18}

CARDIOVASCULAR SYSTEM:

Incidence of death related to myocardial infarction is 2-3 times higher in smokers. Cerebrovascular events like stroke, sub arachnoid hemorrhage is also 2-3 times higher. Almost 90\% of patients are smokers when peripheral vascular disease is concerned.\textsuperscript{23,24}

GASTROINTESTINAL SYSTEM:

Peptic ulcer disease, carcinoma esophagus and Crohns disease have strong association with smoking.\textsuperscript{25}

Carcinoma stomach and pancreas also significant in smokers.

GENITOURINARY SYSTEM:

Increases the risk of infertility, renal and bladder cancer in men. In women cervical carcinoma is 4 times more common than non smokers.\textsuperscript{26}
MISCELLANEOUS SYSTEMS:

Cadmium in tobacco causes cataract

Post menopausal fractures due to reduced bone density

Palmoplantar pustulosis and premature facial wrinkling.\textsuperscript{27,28,29}
Diagrammatic representation of health effects of smoking
MECHANISM OF HARM

1. SMOKERS

2. NON SMOKERS

IN SMOKERS:

LUNGS:-

Toxins like polycyclic aromatic compounds, nitrosoamines, and radioactive polonium causes the following effects that leads to various ill effects in lungs.\(^{30}\)
CARDIOVASCULAR: - increase in systemic vascular permeability to lipids causes atherosclerosis.\textsuperscript{30}

The above chain of events occur in smokers that leads to myocardial infarction, cardiac arrhythmias and sudden cardiac death.

NON SMOKERS: it is variously known as Passive smoking, second hand smoking or environmental tobacco smoking.
EFFECTS DUE TO PARENTAL SMOKING

1. Low birth weight
2. Sudden infant death
3. Pneumonia and bronchitis in children
4. Decreased lung function
5. Asthma in children
6. Increased risk of childhood cancers
7. Learning difficulties in children.\textsuperscript{31,32}

EFFECTS DUE TO ENVIRONMENTAL SMOKING

1. Chest colds and loss of work days
2. Increased risk of lung cancer in spouse
3. Worsening of angina
4. Increased rate of death from ischemic heart disease
5. Decreased productivity and economic burden due to illness among workers exposed to environmental tobacco smoke.\textsuperscript{33,34}

SMOKING CESSATION

Health education regarding ill effects of smoking to general population, health professionals and politicians is the corner stone.\textsuperscript{35}
Strict laws like Norwegian tobacco act 1975 should be implemented to control smoking.

Advertising the financial savings of the individuals who quit smoking is also important. This is done in Norway during 1975 – 1980 Which brought predictable drop in smoking. The Norwegian council on smoking and health also made legislation that offered jobs in asbestos industry only to non smokers. They also raised the price as well as tax on cigarretes. So multi deciplinary approach alone will bring down the incidence of smoking. Early detection of air flow obstruction in smokers offers important tool to educate the community.
CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Definition: chronic obstructive pulmonary disease is defined according to GOLD criteria as airflow limitation that is not fully reversible.\(^5\)

COPD includes the following

1. EMPHYSEMA: Anatomically defined condition in which there is destruction and enlargement of alveoli

2. CHRONIC BRONCHITIS: Clinically defined disease which is associated with chronic cough and phlegm

3. SMALL AIRWAYS DISEASE: Characterized by narrowing of Small bronchioles.

Criteria to diagnose COPD is presence of chronic airflow obstruction.

RISK FACTORS

1. Cigarette smoking: Association between cigarette smoking and COPD is proved absolutely. There is also correlation between FEV1 and pack years of smoking in general population.
2. AIRWAY RESPONSIVENESS

Two hypothesis has been formulated based on airway responsiveness of patients with COPD.

i. **DUTCH HYPOTHESIS**: It states that bronchial asthma, chronic bronchitis and emphysema are variations of the same disease. These are modulated by genetic and environmental factors to produce these distinct disease patterns.
ii. **BRITISH HYPOTHESIS**: It states that asthma and COPD are two different disease entities. Asthma is due to allergic phenomenon and COPD is due to smoking related inflammatory disease.

Validation of these hypothesis awaits analysis of predisposing factors like genetic and environmental factors.

3. **RESPIRATORY INFECTIONS**: This entity awaits to be proven since there is no data available to correlate. These are now important cause of acute exacerbations

4. **OCCUPATIONAL EXPOSURE**: The following occupational exposures have been suggested as risk factors for COPD Coal mining, cotton mill dust and gold Mining.

5. **AMBIENT AIR POLLUTION**: Urban living and biomass combustion in rural areas are proposed but not proven.

6. **PASSIVE OR SECOND HAND SMOKE EXPOSURE**: Maternal smoking is associated with adverse neonatal outcome like low birth weight, reduced lung growth and reduction in post natal lung function.

7. **GENETIC FACTORS**:

   i. Alpha one antitrypsin deficiency: Many protease inhibitors have been postulated among them
M allele is most common associated with normal a1AT

S allele with slightly reduced a1AT

Z allele with severely reduced a1AT

PiZ is known to be either individual with one Z and one null allele or two Z allele and it is the common form of a1AT deficiency.

COPD occurs in earlier age in a1AT deficiency smokers than non smokers.\textsuperscript{36}

Other genes responsible for COPD are MMP12 and HHIP.\textsuperscript{38}

**NATURAL HISTORY OF COPD**

The association of cigarette smoking and lung function depends on duration of smoking, intensity of smoking, baseline pulmonary function of individual and environmental factors.

Reduced levels of FEV1 is closely associated with mortality in COPD.
Early interventions like smoking cessation in young age will provide more morbidity and mortality benefits than measures done after significant decline in pulmonary function.

Genetic and environmental factors play a crucial role along with smoking.
PATHOPHYSIOLOGY

Airflow obstruction in the form of persistent reduction in forced expiratory flow rate is classical finding in patients with COPD.

AIRFLOW OBSTRUCTION:

Also known as airflow limitation which is measured by spirometry uses forced expiratory maneuvers. Key parameters obtained are FEV1 and FVC. Patient with COPD have chronic reductions in FEV1/FVC ratio.

Post bronchodilator FEV1 will show improvements up to 15% which is helpful in differentiating from asthma. In asthma there will be larger response to inhaled bronchodilator.

In initial stages of COPD the airflow abnormality is evident at or below the functional residual capacity. It gives scooped out appearance to lower part of flow volume loop. In advanced disease the curve assumes reduced expiratory flow compared to normal

HYPERINFLATION:

It compensates for airflow limitation but has deleterious effects on lung function by flattening diaphragm.
Diagrammatic representation of effects of hyperinflation on lung function

**GAS EXCHANGE:**

PaO₂ falls below normal range only when FEV₁ is less than 50% of predicted. Rise in PaCo₂ occurs only with FEV₁ values below 25% of predicted.

Ventilation perfusion mismatch occurring in COPD is characteristic as it is non uniform.
Supplemental oxygen is useful in treating hypoxemia due to COPD because shunting is minimal.

**PATHOLOGY**

LARGE AIRWAYS: Mucous gland enlargement, goblet cell hyperplasia and squamous cell metaplasia of bronchial mucosa

SMALL AIRWAYS: Airways <2 mm are major sites for resistance in COPD. Reduction in surfactant secreting type 2 cells increases surface tension.

LUNG PARENCHYMA: Destruction of respiratory bronchioles, alveolar ducts and alveoli results in reduction in gas exchanging air spaces in emphysema. Types of emphysema are cenriacinar and panacinar.

**PATHOGENESIS**

Fibrosis and collagen accumulation around small airways is significant contributor. Schematic representation of chain of events that occur in smokers and leads to COPD is as follows
Prominent steps are

1. Smoking causes recruitment of inflammatory cells to airways
2. Elastase and antielastase hypothesis
3. Extracellular matrix proteolysis
4. Cell death
5. Ineffective repair

CLINICAL PRESENTATION

Majority of smokers are asymptomatic until 50% of their lung volume is lost.

Cough, sputum production and exertional dyspnea are common symptoms in COPD.

Patients usually have symptoms years before and come for medical attention only after worsening.

Physical examination show prolonged expiration and expiratory wheeze.

**Pink puffers** or emphysematous patients are thin and non cyanotic at rest.

**Blue bloaters** or chronic bronchitis patients are heavy and cyanotic

**Hoovers sign**- in advanced disease there is inward movement of rib cage during inspiration.

In severe obstruction the patient will assume **tripod position**.
LABORATORY FINDINGS

1. Pulmonary function testing.

Pulmonary function tests are defined as a series of tests both invasive and non invasive done with standardized equipment.

They are used to identify and quantify many structural and functional abnormalities of the respiratory system.

These include

1. Spirometry

2. Lung volumes by helium dilution or by body plethysmography
   - Tests for ventilatory function

3. Peak Expiratory flow rate using breathometer

4. Pulse oximetry
   - Bedside tests

5. Ventilation –Perfusion scan (V/Q scan)
6. Diffusing capacity for carbon monoxide
   - Tests for diffusion

7. PI max and PE max
   - Test for respiratory muscle function

8. Arterial blood gases

9. Bronchial challenge tests

10. Exercise test

11. Polysomnography
   1. Test for sleep related disorder

12. Other tests
   1. Chest radiograph
   2. Computed tomography of chest
   3. a1AT levels in serum
   4. Molecular genotyping of PI alleles (M,S,and Z)
## GOLD Criteria for COPD Severity

| GOLD Stage | Severity   | Symptoms                                      | Spirometry                                      |
|------------|------------|-----------------------------------------------|-------------------------------------------------|
| 0          | At Risk    | Chronic cough, sputum production              | Normal                                          |
| I          | Mild       | With or without chronic cough or sputum production | FEV\textsubscript{1}/FVC <0.7 and FEV\textsubscript{1} ≥80% predicted |
| IIA        | Moderate   | With or without chronic cough or sputum production | FEV\textsubscript{1}/FVC <0.7 and 50% ≤FEV\textsubscript{1} <80% predicted |
| III        | Severe     | With or without chronic cough or sputum production | FEV\textsubscript{1}/FVC <0.7 and 30% ≤FEV\textsubscript{1} <50% predicted |
| IV         | Very Severe| With or without chronic cough or sputum production | FEV\textsubscript{1}/FVC <0.7 and FEV\textsubscript{1} <30% predicted or FEV\textsubscript{1} <50% predicted with respiratory failure or signs of right heart failure |

*Abbreviation:* GOLD, Global Initiative for Lung Disease.
GOLD: Global Initiative for Obstructive Lung Disease requires FEV1/FVC ratio less than 0.7 post bronchodilator.

CRITERIA FOR COPD SEVERITY:

1. Mild COPD - FEV1/FVC <0.7 and FEV1p> 80%
2. Moderate COPD - FEV1/FVC <0.7 and FEV1p 50% - 80%
3. Severe COPD - FEV1/FVC <0.7 and FEV1p 30% - 50%
4. Very severe COPD - FEV1/FVC <0.7 and FEV1p< 30%
   or
   FEV1p <50% and chronic respiratory failure.

In our study after identifying the patients with COPD the severity is assessed according to above guidelines.
TREATMENT

1. General measures like smoking cessation, oxygen therapy.

2. Bronchodilators – beta agonist, anticholinergics, inhaled corticosteroids

3. Oral glucocorticoids

4. Theophylline

5. N-acetyl cystine

6. a1AT augmentation therapy

7. Pulmonary rehabilitation

8. Lung volume reduction surgery

9. Lung transplantation

10. Mechanical ventilatory support. 36
Figure – Inhalation therapies in COPD according to GOLD guidelines

Use of inhaled therapies

Breathlessness and exercise limitation

- **SABA or SAMA as required**
  - **FEV₁ ≥ 50%**
    - LABA
      - LABA or LAMA as required
      - Consider LABA + LAMA if ICS declined or not tolerated
  - Exacerbations or persistent breathlessness
    - **FEV₁ < 50%**
      - LAMA
        - Discontinue SAMA
        - Offer LAMA in preference to regular SAMA four times a day
      - LABA + ICS
        - In a combination inhaler
        - Consider LABA + LAMA if ICS declined or not tolerated
      - LAMA
        - Discontinue SAMA
        - Offer LAMA in preference to regular SAMA four times a day

Abbreviations:
- SABA: Short-acting β₂ agonist
- SAMA: Short-acting muscarinic antagonist
- LABA: Long-acting β₂ agonist
- LAMA: Long-acting muscarinic antagonist
- ICS: Inhaled corticosteroids

- Offer therapy (strong evidence)
- Consider therapy (less strong evidence)
SPIROMETRY

HISTORY

1800 Hutchinson developed simple water sealed spirometer used measure vital capacity

1930 barach developed kymograph or rotating chart drum that disploted changes in vital capacity as spirogram.

1941 Cournand and Richard described MVV

1947 Tiffeneau described FEV1/IVC ratio as index of airflow limitation called Tiffeneau index

1950 Gaensler used micro along with water sealed spirometer to time FVC1950 Comroe,Dubois and others described technique to estimate alveolar pressure.

1950 late , Hyatt used flow volume curve to display air way function

1955 Leuallen and Fowler described maximal mid expiratory flow rates 25% and 75% now known as FEF25%-75%

1960 Wright and Mckerrow started using peak flow meter in asthma patients
Spirometry is the most commonly performed lung function test. It is described as GOLD STANDARD to diagnose COPD by WHO and GOLD criteria.

**INDICATIONS FOR SPIROMETRY**

1. To diagnose the presence or absence of lung disease

2. To quantify the known pulmonary disease severity

3. To measure the environmental and occupational exposure effects

4. To identify the merits and demerits of therapy

5. To assess the risk factors of proposed surgical procedures in view of pulmonary disease

6. To evaluate morbidity or impairment for legal or insurance evaluation

7. To evaluate data for epidemiological and clinical research in the field of lung diseases

**CONTRAINDICATIONS TO SPIROMETRY**

**ABSOLUTE**

1. Acute coronary event, myocardial infarction in last 30 days

2. Recent thoraco abdominal or ophthalmic surgery
3. Recent cerebrovascular event

4. Poorly controlled hypertension

5. Underlying aortic and cerebral aneurysm

6. Recent pneumothorax

RELATIVE

1. Head ache
2. Stress incontinence
3. Confusion
4. Facial, abdominal and chest pain
5. Dementia

LUNG VOLUMES AND DEFINITIONS

The quantity of air that moves in and out the respiratory tract during each respiratory cycle is called **Tidal volume (TV)**

The further volume of air that can be inspired after a normal tidal inspiration is called **Inspiratory reserve volume (IRV)**

The further volume of air that can be exhaled after a normal tidal expiration is called **Expiratory reserve volume (ERV)**

The maximal amount of air that can be exhaled after a maximal
inspiration is called **Vital capacity (VC)**. \( VC = TV + IRV + ERV \).

The amount of air that relics in the lungs after maximal expiration is **Residual volume (RV)**. Even with forceful effort it cannot be expired.

The quantity of air that remains in the lung after maximal inspiration is termed as **Total lung capacity (TLC)**. \( TLC = FRC + TV + IRV = VC + RV \)

The volume of air exhaled per minute is called **Minute volume**.

**Maximal voluntary ventilation** (Maximum breathing capacity) is the highest amount of air that can be exhaled in a 15 second gap by voluntary effort. This is uttered as liters per minute by multiplying by 4.

The quantity of air that can be forcefully exhaled in 1 second is termed as **Forced expiratory volume 1 (FEV\(_1\))**

The maximum amount of air that can be forcefully exhaled is termed as **Forced vital capacity (FVC)**

\( FEV_1/FVC \) is expressed as a percentage.
The standard volume of air that is exhaled during the mid portion of FVC is termed as **Mid expiratory flow (MEF25 - 75)**

The peak flow rate during expiration is called as **Peak expiratory flow rate** (PEFR) - normal range is 400-600 L/min

It is a consistent method of differentiating obstructive airway disorders and restrictive lung diseases.

Precise spirometry can only be performed with proper training and adequate motivation of patients.
LIMITATIONS

1. It requests a well trained technician and patient support for accuracy of test

2. There is a little variability in normal predictive value

3. It should be interpreted in the milieu of a proper history, physical examination and added diagnostic tests.

ADVANTAGES

- Simple & supportive in reaching diagnosis
- Used as a first stride in detecting lung function abnormalities &

Answer important questions such as:

Is there airflow limitation? If so how severe is it?

Is there a response to bronchodilator therapy? If so how much?

Is there barrier present down the major airways?

Is it intra or extra thoracic?
Figure – Lung volumes and capacities
PERFORMING

SPIROMETRY

Preparation

1. Equipment:
   - Checking for leaks
   - Fresh mouth piece
   - Checking recording equipment
   - Performing calibrations

2. Patient
   - The height and weight are measured
   - Any contraindications should be ruled out
   - The procedure is explained to the individual and should be demonstrated
   - The person should sit erect and look straight ahead to avoid stretching of trachea.

Basic

Components
   - Maximal inspiration
   - Maximal expiration ('blast' expiration)
• Continued expiration until maximal amount of air is exhaled up to residual volume - at least a 6 seconds of exhalation in adults

Correct maneuver

• The exhaled volume should be delivered from the level of maximum inspiration with maximal exertion.

• The maneuver is started immediately with a 'blast'. There should be rapid rise to peak flow, and the attempt is sustained.

• The exhalation should continue to the residual volume. (exhalation continued up to vital capacity).

It should not be troubled by coughing or sneezing.

There should not be any leak from mouthpiece
ATS/ERS recommendations are as follows:

| Parameter                        | Description                                                                                                                                 |
|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| FVC minimum duration             | 6 sec (3 sec for children) or plateau in the volume time curve, subject cannot or could not continue to exhale                                |
| FVC end of test criteria         | Subject cannot or should not continue further exhalation or the volume time curve shows an obvious plateau or the forced exhalation is of reasonable duration |
| FVC maximum number of maneuvers  | 8, both in adults and children                                                                                                           |
| FVC maneuver acceptability       | Unsatisfactory start of expiration                                                                                                       |
|                                  | Back extrapolated volume > 5% of FVC or 150 ml, Whichever is greater                                                                      |
|                                  | Coughing which interferes with measurement of FEV1 and/or FVC.                                                                              |
|                                  | Early termination of expiration                                                                                                           |
|                                  | Valsalva maneuver                                                                                                                         |
|                                  | A leak                                                                                                                                     |
|                                  | An obstructed mouth piece                                                                                                                 |
|                                  | Effort that is not maximal                                                                                                                |
| FVC and FEV1 reproducibility     | The largest and second largest FVC and FEV1 should not differ by 150 ml                                                                  |
NORMAL VALUES

The outcome of Spirometry are reported as **absolute** (measured) values and as predicted percentage of normal values. Normal values will depend on the individual's age, sex, ethnicity and height. There is no universal standardization for normal values and the values that differ from one laboratory to the other.

Thus normal reference values were obtained by performing tests in thousands of people based on age, sex, ethnicity and height.
FACTORS DETERMINING LUNG VOLUMES

- HEIGHT - shorter persons have lesser lung volumes

- GENDER - females have lesser lung volumes than males

- AGE – lung volume keeps on rising in children, steady in adults and as age advances the ERV decreases and RV,FRC increases.

- ETHNICITY – values vary for Africans, Asian, and White populations
Normal value = 80 - 120% of predicted

SPIROMETRY REPORT: typically consists of absolute numerical values or graphical depiction of the same or a mixture of both.

Common Numerical Values

- FEV1
- FVC
- FEV1/FVC
- PEFR
- FEF 25-75%

Graphical representation

- Time - Volume curve
- Flow - Volume loop
FEV1 (Forced Expiratory Volume in the first second) is the volume expired in the first second of the test.

FEV1% = FEV1/FVC X 100.

roughly 80% of all the air is exhaled out in the first second by a healthy individual out of their lungs during the FVC exercise.

FEV1% will be reduced in case of barrier in upper airways.

Too high FEV1% is indicative of restriction.
**OBSTRUCTIVE PATTERN:**

Either intrathoracic or extrathoracic.

\[
\text{FEV1 } \% \quad = \quad \text{observed FEV1 / predicted FEV1 } < \quad 80\%
\]

\[
\text{FEV1 / FVC } \% \quad = \quad \text{observed FEV1 / observed FVC } < \quad 75\%
\]

Severity of obstruction can be graded based on FEV1% based on GOLD criteria as 80% mild, 80%-50% moderate, 50%-30% severe,<30% very severe

FEV1 /FVC may erroneously be normal due to air trapping which cause markedly

Reduced FVC in persons with moderate to severe obstruction.

FEV1 / FVC will be less than 70-80% in elderly due to age related decline without major obstruction. Early stages of neuromuscular disorders can cause low

FEV1 /FVC due to reduction in FEV1. In obstructive disorders MMFR, PEFR are reduced to less than 75% of their predicted values.
CLASSIFICATION BASED ON FEV1 AND FVC VALUES

RESTRICTIVE PATTERN:

Pleural and parenchymal fibrotic diseases, chest wall diseases

FVC % = \frac{\text{observed FVC}}{\text{predicted FVC}} < 75\%

Reduced FVC is not sufficient for diagnosis but it can suggest the probability of restrictive abnormality. It mainly depends on patient’s performance. Fallaciously low values of FVC occurs in moderate to
severe obstruction. Restrictive diseases has to be confirmed by extent of
Residual volume (RV) and Total Lung Capacity (TLC) by Helium
dilution technique and Body Plethysmography. However interpretation of
spirometric data with clinical correlation is sufficient for all practical
purposes.
INTERPRETATION OF SPIROGRAM

Acceptable spirogram

Is FEV1/FVC ratio low? <70%?

Yes → Obstructive disorder

Is FVC low? <80%?

Yes → Hyperinflation vs combined defect

Further testing (lung volumes)

No → Pure obstruction

Reversible w/ use of B2 agonist

Yes: asthma

No: COPD

No → Is FVC low? <80%?

Yes → Restrictive disorder

Further testing

No → Normal spirometry results
The Flow-Volume loop explained:

The spirometric proportions are recorded in a graphic representation called Flow–Volume loop. It has volume in X axis and time in Y axis. At point zero both flow and time are zero. Once the patient exhales it reaches a crest within 150ms which is called Peak Expiratory Flow (PEF). This peak flow represents the air exhaled from the proximal larger airways. After the peak the curve rapidly descends and reaches 25%, which is called FEF 25%.
After 75% of the air exhaled it reaches FEF 75%.

The mean flow between 25% and 75% is called FEF 25-75%. This gives a measure of airflow in the medium sized airways. This parameter is the first to decline in most of the respiratory diseases. Almost 90% of the air is exhaled in the first second. FVC is achieved if the flow reaches zero.

**Obstructive Airway Disease:**

In obstructive airway diseases like COPD and Asthma the small airways are narrowed and flow volume loop shows a concave pattern or scooped out pattern.
The PEF is normal since the air in larger airways is expelled easily. Since smaller airways are narrowed the air is expelled slowly leading to a low flow. This causes sharp fall in the flow volume loop. Both FEV1 and FEF 25-75 are low.

Obstructive airway disease:

Fig: low FEV1
Restrictive Lung Disease:

Restrictive lung diseases are characterized by low total lung volume. Spirometry can point out the probability of restriction and it has to be established by other methods. Since there is no obstruction the curve of flow volume is normal but the FVC is reduced. Peak Expiratory Flow can be normal or low.

Fig: Low FVC with normal shape in restrictive lung disease:
Fig: Too low FEV1 in restrictive lung disease in volume - time curve.

UPPER AIRWAY OBSTRUCTION (UAO):

The following are the characteristics of upper airway obstruction.

- Midpoint maximal inspiratory flow is FIF 50% < 100 L/min
- Ratio of midpoint maximal expiratory flow to midpoint maximal inspiratory flow: FEF50% > 1/FIF50%
- Ratio of forced expiratory volume in 1 second to peak expiratory flow rate FEV1/PEFR > 10 ml /L/minute
- Ratio of forced expiratory volume in 1 second to forced expiratory volume in 0.5 seconds FEV1/FEV0.5 > 1.5

Extra thoracic obstruction can be classified into following categories.

1. Extra thoracic Obstruction

- variable

The obstruction is more significant during inspiration and expiration is normal. This occurs due to the fact that during expiration the obstruction is overcome by the force of expiration. In flow –volume loop the inspiratory part is flattened and expiratory part is normal.

e.g : laryngeal tumours, extrathoracic goiter, paralysis of vocal cord.
2. *Intra thoracic Obstruction* - variable

In intra thoracic obstruction, during inspiration the trachea is sucked out and during expiration it causes partial obstruction. Inspiratory part of the flow–volume loop is normal and the expiratory part is flattened.

![Flow Volume Loop]

2. **Fixed obstruction of the Large Airways:**

The obstruction can be both extra thoracic and intra thoracic. Both inspiratory and expiratory part of the flow–volume loop are flattened.

e.g. intra tracheal tumours, tracheal stenosis.\(^{37}\)
TROUBLESHOOTING: Common cause for inconsistent spirometry is patient technique. Other causes are as follows

1. Incomplete inspiration and sub optimal expiration

2. Delayed maximal effort that under estimates FEV1

3. Inadequate emptying of lungs occurs commonly in COPD

4. Incomplete sealing of lips around mouth piece underestimates FVC and FEV1

5. Exhalation through nose

6. Coughing

7. Mouth piece obstruction by teeth
AIMS AND OBJECTIVE
AIMS AND OBJECTIVE

1. Early detection of COPD in asymptomatic smokers by using spirometer in south India.

2. To correlate BMI, smoking index and age of onset of first smoke with FEVI/FVC Ratio.

3. To Study the relationship between SI and FEV1/FVC ratio with severity of COPD.
MATERIALS AND METHODS
MATERIALS AND METHODS

PLACE OF STUDY:

MAHATMA GANDHI MEMORIAL GOVERNMENT HOSPITAL attached to KAP VISWANATHAM GOVERNMENT MEDICAL COLLEGE, TIRUCHIRAPPALLI in southern region of India

DEPARTMENT IN WHICH STUDY CONDUCTED:

Department of General Medicine

PERIOD OF STUDY: From JANUARY 2014 to August 2014

STUDY DESIGN: A prospective descriptive cross sectional study

ETHICAL COMMITTEE: Institutional ethical committee approval obtained. The study population was well explained about the study and its purpose in local language. Informed and written consent obtained from study population
**INCLUSION CRITERIA:**

1. Subjects with history of smoking and age above 25 years
2. No significant respiratory symptoms
3. Regular smokers
4. Willing to undergo spirometry
5. Willing to give consent to participate in the study

**EXCLUSION CRITERIA:**

1. Subjects with smoking cessation
2. History of respiratory disease like tuberculosis, bronchial asthma or occupational lung disease
3. On inhaled bronchodilators or corticosteroids
4. Diabetes mellitus, hypertension and coronary artery heart disease
5. Chest wall and vertebral deformities like pectus, kyphosis, scoliosis
6. Inadequate spirometry like air escape, failure to reach plateau are excluded

**STUDY GROUP:**

Patients attending the out patient department of tertiary care hospital, MAHATMA GANDHI MEMORIAL GOVERNMENT HOSPITAL attached to KAP VISWANATHAM GOVERNMENT MEDICAL COLLEGE, TIRUCHIRAPALLI in southern region of India
**SAMPLE SIZE:** Calculated from prevalence in North Indian and Madras study. Total number of subjects included was 174. All are men with history of smoking

**MATERIALS:**

1. EASY ONE spirometer
2. Disposable mouth piece
3. Weighing scale
4. Stadiometer
5. Printed materials explaining ill effects of smoking and benefits of smoking cessation regarding health and financial concerns

**SPIROMETER**

Easy one spirometer. It is a handy spirometer based on ultra sonic flow sensor system. The benefit of this spirometer is disposable flow tube can be inserted between transducers that prevents cross infectivity. in view of the fact that the tube acts a transparent barrier sorting out the airflow and transducer it does not require calibration. Also this spirometer is not affected by the composition of gas is added advantage. This type of compact, microprocessor integrated spirometer is recommended in various studies for screening of smokers for COPD. In our study we used same type of instrument which can be connected to computer to get the report.
METHODOLOGY

After getting consent from subjects they were given short lecture using printed modules in a language Tamil and demonstration of spirometry is done by the technician who does the procedure. Quantum of smoking was calculated using smoking index. Smoking index: number of cigarettes or bidies per day multiplied by number of years of smoking. Smoking index selected because number of cigarettes,bidis vary depending upon the manufacturer hence it is more
appropriate than pack years.

Height, weight and BMI was considered. They were subjected to spirometry 15 mins after 400 mcg of salbutamol nebulisation as per GOLD criteria. The predicted and measured values of FEV1, FVC, FEV1/FVC, PEFR, FEF 25-75 for all the patients were recorded. Minimum of three trials and maximum of eight trials done for each subject based on guidelines from American Thoracic Society.

The data were analyzed as per GOLD criteria and the subjects classified as mild, moderate, severe and very severe air flow obstruction using statistical test.
RESULTS

FIGURE - 1 Age distribution of smokers in percentage

28-38 years 28.7% (n=50)

39-49 years 38.5% (n=68)

50-60 years 29.3% (n=51)

61-71 years 2.8% (n=5)
BMI – Body mass index

1. <18.5 5.17% (n=9)
2. 18.5-24.9 76.43% (n=134)
3. 25.0-29.9 13.21%(n=23)
4. 30.0-34.9 4.02% (n=8)
FIGURE - 3 Smoking index distribution in smokers

| SI     | NUMBER OF SMOKERS | PERCENTAGE |
|--------|-------------------|------------|
| <100   | 7                 | 4.02%      |
| 101-299| 133               | 76.43%     |
| >300   | 34                | 19.43%     |
1. Youngest age is 16 years

2. Maximum number observed is at 18 years
Normal spirometry – 82.18%(n=143)

Obstruction - 17.81%(n=31)

Among obstructive pattern

Mild obstruction - 61.29%(n=19)

Moderate obstruction- 38.7%(n=12)
| PARAMETERS (N=174) | MEAN(SD)       | MINIMUM | MAXIMUM |
|-------------------|----------------|---------|---------|
| AGE               | 44.9943 (8.794) | 28      | 65      |
| ONSET             | 20.65 (2.634)   | 16      | 26      |
| BMI               | 22.6925 (3.101) | 16.5    | 32      |
| SI                | 226.821 (77.315)| 80      | 450     |
| FVCp              | 87.31 (58.383)  | 58      | 822     |
| FEV1p             | 79.97 (16.248)  | 51      | 152     |
| FEV1/FVCp         | 98.55 (17.961)  | 60      | 139     |
| MEF 25-75         | 64.4 (31.458)   | 11      | 191     |
| MEF 75            | 68.68 (23.448)  | 18      | 137     |
| MEF 50            | 66.66 (24.668)  | 22      | 133     |
| MEF 25            | 59.90 (32.588)  | 7       | 247     |
| PEF               | 69.74 (22.198)  | 24      | 128     |
| FVC m             | 3.2059 (.78459) | 1.33    | 5.46    |
| FEV1m             | 2.7059 (.68959) | 1       | 4.53    |
| FEV1/FVC m        | .7755 (.07193)  | 0.18    | 0.85    |
Onset - age of first smoke

BMI - Body mass index

SI - Smoking index

FVCp - Forced vital capacity (Percent)

FEV1p – Forced expiratory volume in 1 second (percent)

MEF 25-75 – Mid expiratory flow

PEF - Peak expiratory flow

FVCm - Forced vital capacity (measured)

FEV1m – Forced expiratory volume in 1 second (measured)
| PARAMETERS (N=174) | MEAN(SD)          | p VALUE |
|------------------|------------------|---------|
| AGE              | 44.9943 (8.794)  | 0.075   |
| ONSET            | 20.65 (2.634)    | 0.001***|
| BMI              | 22.6925 (3.101)  | 0.101   |
| SI               | 226.821 (77.315) | 0.001***|
| FVCp             | 87.31 (58.383)   | 0.001***|
| FEV1p            | 79.97 (16.248)   | 0.002** |
| FEV1/FVCp        | 98.55 (17.961)   | 0.018*  |
| MEF 25-75        | 64.4 (31.458)    | 0.065   |
| MEF 75           | 68.68 (23.448)   | 0.651   |
| MEF 50           | 66.66 (24.668)   | 0.062   |
| MEF 25           | 59.90 (32.588)   | 0.035*  |
| PEF              | 69.74 (22.198)   | 0.564   |
| FVC m            | 3.2059 (.78459)  | 0.054   |
| FEV1m            | 2.7059 (.68959)  | 0.322   |
| FEV1/FVC m       | .7755 (.07193)   | 0.001***|

* is p value < 0.05

** is p value < 0.01

*** is p value < 0.001
### TABLE 3A

| CHI SQUARE | ONSET | FVCm | FVCp | FEV1m | FEV1p | FEV1FVCm | FEV1FVCp |
|------------|-------|------|------|-------|-------|----------|----------|
| 64.613a    | 107.609b | 77.59c | 87.33b | 180.39d | 108.46e | 79.36d   |
| 10         | 97     | 52   | 97   | 46    | 21    | 46       |
| 0.001***   | 0.217  | 0.012* | 0.749 | 0.001*** | 0.001*** | 0.002** |

### TABLE 3B

| CHI SQUARE | PEF | MEF25-75 | MEF75 | MEF50 | MEF25 | BMI | SI | AGE |
|------------|-----|----------|-------|-------|-------|-----|----|-----|
| 69.86f     | 61.55g       | 71.07h    | 85.03i | 98.41j | 108.89k | 240.25l | 57.72m |
| 67         | 80 | 68       | 71    | 78    | 83    | 39   | 35  |
| 0.382      | 0.938 | 0.376    | 0.122 | 0.059 | 0.03* | .001*** | .009** |

*is p value <0.05

**is p value <0.01

***is p value < 0.001
|        | HEIGHT | WEIGHT | ONSET | FVCm | FVCp | FEV1m | FEV1p | FEV1FVCm | FEV1FVCp | PEF | MEF25-75 | BMI | SI | AGE |
|--------|--------|--------|-------|------|------|-------|-------|-----------|----------|-----|---------|-----|----|-----|
| HEIGHT | 1      |        |       |      |      |       |       |           |          |     |         |     |     |     |
| p VALUE|        |        |       |      |      |       |       |           |          |     |         |     |     |     |
| WEIGHT | .391***| 1      |       |      |      |       |       |           |          |     |         |     |     |     |
| p VALUE| 0.001  |        |       |      |      |       |       |           |          |     |         |     |     |     |
| ONSET  | -0.013 | -0.046 | 1     |      |      |       |       |           |          |     |         |     |     |     |
| p VALUE| 0.862  | 0.546  |       |      |      |       |       |           |          |     |         |     |     |     |
| FVCm   | .482***| .192*  | -0.034| 1    |      |       |       |           |          |     |         |     |     |     |
| p VALUE| 0.001  | 0.011  | 0.661 |      |      |       |       |           |          |     |         |     |     |     |
| FVCp   | -0.057 | -0.032 | 0.123 | -0.034| 1    |       |       |           |          |     |         |     |     |     |
| p VALUE| -0.034 | 0.672  | 0.106 | 0.658 |      |       |       |           |          |     |         |     |     |     |
| FEV1m  | .460***| .243***| -0.085| .956***| -0.042 | 1    |       |           |          |     |         |     |     |     |
| p VALUE| 0.001  | 0.001  | 0.268 | 0.001 | 0.586 |       |       |           |          |     |         |     |     |     |
| FEV1p  | 0.014  | 0.044  | 0.069 | 0.002 | 0.049 | 0.007 | 1     |           |          |     |         |     |     |     |
|       | p VALUE | 0.859 | 0.567 | 0.369 | 0.979 | 0.521 | 0.923 |
|-------|---------|-------|-------|-------|-------|-------|-------|
| FEV1FVCm | 0.044 | 0.063 | 0.021 | 0.084 | -0.125 | 0.126 | .257*** | 1 |
| p VALUE | 0.565 | 0.406 | 0.78  | 0.272 | 0.099 | 0.098 | 0.001 |
| FEV1FVCp | -0.077 | -0.021 | -0.042 | -0.088 | .229** | -0.088 | .254*** | .460*** | 1 |
| p VALUE | 0.312 | 0.787 | 0.583 | 0.25  | 0.002 | 0.25  | 0.001 | 0.001 |
| PEF    | 0.128 | .193* | 0.008 | .154* | -0.135 | .167* | .377*** | .345*** | .353*** | 1 |
| p VALUE | 0.092 | 0.011 | 0.916 | 0.043 | 0.075 | 0.028 | 0.001 | 0.001 | 0.001 |
| MEF25-75 | 0.078 | -0.004 | 0.018 | 0.091 | -.151* | 0.089 | .383*** | .313*** | .704*** | .485*** | 1 |
| p VALUE | 0.307 | 0.961 | 0.81  | 0.234 | 0.046 | 0.241 | 0.001 | 0.001 | 0.001 | 0.001 |
| BMI    | -.259*** | .756*** | -0.037 | -0.106 | 0.003 | -0.039 | 0.05  | 0.038 | 0.039 | .167* | -0.047 | 1 |
| p VALUE | 0.001 | 0.001 | 0.633 | 0.163 | 0.973 | 0.606 | 0.511 | 0.616 | 0.606 | 0.028 | 0.535 |
| SI     | -0.006 | -0.036 | -0.009 | -.187* | 0.133 | -.225** | -.158* | -.476*** | -.406*** | - | - | 1 |
| p VALUE | 0.94  | 0.636 | 0.902 | 0.014 | 0.08  | 0.003 | 0.038 | 0.001 | 0.001 | 0.001 | 0.004 | 0.593 |
|   |   |   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|---|---|
| AGE | -0.197** | -0.13 | 0.069 | -0.387** | 0.114 | .478*** | -0.058 | -0.300*** | -0.04 | -0.088 | -0.046 | 0.017 | .616*** | 1  |
| Pvalue | 0.009 | 0.088 | 0.364 | 0.003 | 0.135 | 0.001 | 0.445 | 0.001 | 0.6 | 0.247 | 0.543 | 0.82 | 0.001 |

* is p value < 0.05

** is p value < 0.01

*** is p value < 0.001
SUMMARY
SUMMARY

FIGURE 1 Shows

Age distribution of smokers in percentage

39-49 years 38.5% (n=68) is commonly observed data

FIGURE 2 shows

BMI distribution of smokers in percentage

18.5-24.9  76.43% (n=134)

FIGURE 3 shows

Smoking index distribution in smokers

SI 101-299 in 76.43% (n=133)

FIGURE 4 shows

Age of first smoke among smokers

1. Youngest age is 16 years
2. Maximum number observed is at 18 years

FIGURE 5 shows

Distribution of obstructive lung disease in spirometry

Normal spirometry – 82.18% (n=143)
Obstruction - 17.81% (n=31)

Among obstructive pattern

Mild obstruction - 61.29% (n=19)

Moderate obstruction - 38.7% (n=12)

**TABLE 1**

Distribution of parameters in mean and standard deviation

Age group – 44.99(8.79) in years

Age of first smoke - 20.65 (2.634) in years

BMI – 22.69(3.10)

SI - 226.82 (77.31)

FVCp – 87.31( 58.38)

FEV1p -79.97(16.24)

FEV1FVCp – 98.55(17.96)

MEF 2575 – 64.4(31.45)

MEF75 – 68.68 (23.44)

MEF50 – 66.66(24.66)

MEF25- 59.9(32.58)
FEV1m – 2.70(.071)

FEV1FVCm - 0.77(0.071)

FVCm – 3.2 (0.78)

**TABLE 2**

One sample T test

FEV1FVCp and MEF25 have p value < 0.05

FEV1p has p value <0.01

Age of first smoke, SI,FVCp and FEV1FVCm have p value <0.001

**TABLE 3**

Chi square test

BMI - 108.46 (p value <0.05 )and FVCp -77.59(p value <0.05)

Age - 57.724(p value < 0.01 ) and FEV1FVCp -79.386(p value 0.002)

Age of first smoke , SI -240.25, FEV1p- 180.39 and FEV1FVCm -108.46

p value < 0.001
TABLE 4

| Correlation coefficient |
|-------------------------|
| SI has significant negative correlation with FEV1m _0.225(p 0.003), FEV1p _0.158 (p 0.03), FEV1FVCm _0.476(p0.001), FEV1FVCp _0.406 (p 0.001), PEF _0.256 (p 0.001), MEF 25-75 _0.216(P 0.004) |
| FEV1FVCm has significant positive correlation with FEV1p 0.257 (p 0.001) |
| FEV1FVCp has significant negative correlation with _0.229 (p 0.002) and significant positive correlation with FEV1p 0.254 (p 0.001), FEV1FVCm 0.460 (p0.001) |
| MEF 25-75 has significant positive correlation with FEV1p 0.383(p 0.001), FEV1FVCm 0.313 (0.001), FEV1FVCp 0.704 (p 0.001), PEF 0.485 (p 0.001) |
DISCUSSION
DISCUSSION

This study was conducted for earlier detection of COPD in smokers even before the occurrence of symptoms and signs of obstructive lung disease. The diagnostic criteria used for case finding is as specified in GOLD guidelines. The portable spirometer (Easy one) was used to perform the spirometry. The population in the study group is representative of patients attending the outpatient department in the tertiary care hospital Tiruchirappalli, South India. The prevalence of COPD in this population is 10.2%. The prevalence of smoking has increased and 50% of male smoke cigarette or bidis. Our aim is to detect the presence of COPD earlier in asymptomatic smokers and to correlate the severity of obstructive pattern with SI.

All the participants were male. Since female smoking is not socially accepted in this region only a little proportion smoke. It was ensured that all the participants continue to smoke and does not have respiratory symptoms and signs during the study. Occupational history suggestive of exposure to lung disease have been excluded from the study. Most of them were sales representatives, vendors and auto/taxi drivers.

All are subjected to 400 mcg salbutamol nebulisation fifteen minutes prior to spirometry as per GOLD guidelines. Spirometry was
performed by single technician by demonstrating technique before study. Participants were well informed with printed material regarding ill effects of smoking and benefits of smoking cessation.

The parameters collected were age of first cigarette, BMI, SI, FEV1, FEV1/FVC both measured and percent, MEF25-75, MEF75, MEF50 and MEF 25. The results were statistically analyzed.

**AGE:** The mean age was 44.994 (8.794). Most of them were between 39-49 years (n=67) 38.5%. Youngest age in this study is 28 years. Age group 61-71 years is only 2.87% (n=5). Significant negative correlation with FVCm -0.387(p 0.003), FEV1m -0.478(p 0.001), FEV1/FVCm -0.300(p 0.001). This correlates well with Natural history pattern of COPD in which as the age advances the severity of disease progresses as explained by Fletcher and Peto curve. Less number of patients in >60 years is probably due to occurrence of symptoms as age advances and our study included only asymptomatic patients.

**BMI:** The mean BMI was 22.6925(3.1010). About 76.43(n=133) were in 18.5-24.9 BMI range. Underweight noted only in 5.172%(n=9) probably our study included only asymptomatic population of smokers. Since most of the participants are middle aged working group they were in BMI range of normal to overweight 89.64% (n=140). There is no correlation of BMI with severity of obstructive pattern in our study.
**SMOKING INDEX:** About 78.735% (n=137) participants had moderate SI i.e 100-300. Severe SI observed in 21.26%(n=37). SI and age has significant positive correlation coefficient 0.616(p 0.001) which is consistent with previous studies. SI and FEV1/FVC ratio both m and p has significant negative correlation coefficient (p 0.001) i.e SI increases FEV1/FVC ratio decreases. Moderate obstruction had SI of 400 (88.25) and mild obstruction had SI of 310(66.50). SI also has significant negative correlation coefficient (p 0.001) with MEF 25-75 which is again consistent with presence of small airway disease in smokers with COPD. This parameter was less correlated in previous north Indian study.

FEV1m_ 0.225(p 0.003) , FVCm _0.187(0.01) alone had correlation with SI for diagnosis of obstructive lung disease. When percentage is considered they does not correlate. Thus FEV1/FVC ratio is gold standard for screening presence of airflow limitation in smokers as indicated in study Stralelis G, et al and Zielinski et al. is consistent with our study.

Age of first smoke: Majority started smoking around 20 years. About 1/5 th (n=37) 19.54 % started to smoke at 18 years. Age of first smoke does not have any correlation with obstructive lung disease in our study(p=.839). It is the quantity of smoke and not the duration of smoke
correlates with severity of airflow limitation. Previous studies also given the same report.

**FVC:** It has also got significant negative correlation coefficient \((p \leq 0.001)\) with FEV1/FVC ratio. These are well established in various studies and reproduced in our study also.

**FEV1:** Significant positive correlation coefficient \((p \leq 0.001)\) with FEV1/FVC, MEF 25-75 which is consistent from previous studies. According to GOLD criteria 19/174 had mild and 12/174 had moderate obstruction pattern. All the participants with obstructive spirometry are asymptomatic during study. But when only FEV1 value is considered 57.47\% \((n=100)\) had FEV1 >80. 42.52\% \((n=74)\) had FEV1 50-80\. So in determining the obstructive pathology we need FEV1/FVC or FEV1/FEV6. FEV1 alone is not useful as screening criteria for diagnosis of COPD in asymptomatic smokers.

**FEV1/FVC:** Airflow limitation with FEV1/FVC ratio <70 was noted in 17.816\%(n=31). Out of which when applied to GOLD guidelines mild obstruction noted in 61.2903\%(n=19). Moderate obstruction seen in 38.7096\%(n=12). None of them had severe or very severe obstruction. FEV1/FVC has Significant positive correlation coefficient \((p \leq 0.001)\) with FEV1 and MEF25-75. It has also got significant negative correlation coefficient \((p \leq 0.001)\) with SI and FVC.
MEF25-75: has Significant positive correlation coefficient (p 0.001) with FEV1p and FEV1/FVCm, FEV1/FVCp ratio. It has also got significant negative correlation coefficient (p 0.001) with SI. This parameter is less correlated in previous trials used for screening of COPD. This parameter needs further large trials.
CONCLUSION
CONCLUSION

1. The most common age of first smoking is 18 years and all participants had started smoking by 26 years.
2. The youngest age of first smoking is at 16 years.
3. The age of first smoking does not have significance with airflow limitation.
4. The most common age group found is 39-49 years.
5. The most prevalent BMI is 18.5-24.9 and does not have significance in respect to airflow obstruction.
6. SI has significant negative correlation with FEV1/FVC and Significant positive correlation coefficient with age.
7. The quantum of smoking correlates with severity of airflow obstruction as indicated by SI.
8. There is 17.8% of asymptomatic smokers have airflow limitation in the form of obstructive lung disease.
9. There is 61.29% of asymptomatic smokers had mild COPD and 38.7% had moderate COPD as per GOLD guidelines.
10. The FEV1/FVC ratio as a screening tool to detect the presence of COPD in asymptomatic smokers is established.
11. Handheld in office spirometry is useful for screening the smokers for presence of airflow obstruction before significant symptoms.
12. MEF 25-75 also has significant positive correlation coefficient with FEV1/FVC ratio and significant negative correlation with SI.
LIMITATIONS AND RECOMMENDATIONS

1. The period of study is low, large data would have been collected if done for long time.
2. Serial spirometry not done on same participant since it is cross sectional study
3. Study group is just adequate
4. History regarding occupational exposure is not probed in depth
5. Non smokers as control group not done
6. Environmental tobacco smoking and genetic predisposition to COPD are not ruled out.
7. Economic burden of individual due to smoking is not calculated
8. MEF 25-75 value needs further large trials to use as earlier tool for airflow limitation
9. Regular use of hand held spirometer by primary care physician is recommended to screen airflow limitation in asymptomatic smokers
1. Muray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Gloral Burden of Disease Study. *Lancet* 1997: 349:1498-504

2. Jindal SK, Aggarwal AN. A review of population studies from India to estimate national burden of Chronic obstructive lung disease and its association with smoking. *Indian J Chest Dis Allied Sci* 2001;43:139-147.

3. Mannino DM, Gagnon RC, Petty TL. Obstructive lung disease and low lung function in adults in the United States: data from National Health and Nutrition Examination Survey. 1988-1994. *Arch Intern Med* 2000: 160; 1683-89

4. Gorecka MD, Bednarek M, Nowinski A, et al. Diagnosis of airflow limitation combined with smoking cessation advice increases stop smoking rate. *Chest* 2003;123:1916-1923.

5. Global Initiative for Chronic Obstructive Lung Disease (COPD). Global strategy for the diagnosis, management and prevention of COPD: NHLBI/WHO Workshop Report. Bethesda: National Heart, Lung and Blood Institute; Publication No. 02-3659. Updated 2006

6. Crofton and Douglas’s Respiratory Diseases, 5e, vol 1, Blackwell Science, 2002, p311-323, 616-696
7. Fletcher C, Peto R. The natural history of chronic airflow obstruction. *Br Med J* 1977;1:1645-48

8. Pietinalho A, Innula VL, Sovijarvi ARA, et al. Chronic bronchitis and chronic obstructive pulmonary disease: the Finnish Action Programme, interim report. *Respir Med* 2007;101:1419-25

9. R. Stratelis G, Jakobsson P, Molstad S, Zetterrrrstrom O. Early detection of COPD in primary care: screening by invitation of smokers aged 40-55 years. *Br J General Practice* 2004;54: 201-6.

10. Kohansal R, Martinez-Camblor P, Agusti A, et al. The natural history of chronic airflow obstruction revisited: an analysis of the Framingham offspringing cohort. *Am J Respir Crit Care Med* 2009;180:3-10.

11. Connett JF, Bjornson-Benson WM, Daniels K. Recruitment of participants in the Lung Health Study: Assessment of recruiting strategies: Lung Health Study Research Group. *Control Clin Trials* 1993:14;38S-51

12. Zielinski J, Bednarek M. Early detection of COPD in a high-risk population using spirometric screening. *Chest* 2001;119:731-736

13. P.L. Enright, M. Studnicka, J. Zielinski, Spirometry to detect and manage chronic obstructive pulmonary disease and asthma in the primary care setting Eur Respir Mon, 2005, 31, 1–14
14. MS Barthwal, S Singh. Early detection of Chronic obstructive pulmonary disease in asymptomatic smokers using spirometry, JA PI, Mar 2014, Vol 62, p238-242

15. Johan Buffels, MD; Jan Degryse, MD, PhD; Jan Heyrman, MD, PhD; and Marc Decramer, MD, PhD, Office Spirometry Significantly Improves Early Detection of COPD in General Practice, The DIDASCO Study

16. Thiruvengadam KV, Raghava TP, Bharadwaj KV. Survey of prevalence of chronic bronchitis in Madras city. In: Viswanathan R, Jaggi OP (eds).

17. Jindal SK and Malik SK, Smoking index a measure to quantify cumulative smoking exposure, Lung India (1988), Vol. No.4(195-196).

18. Doll R, Peto R, Hall E, Wheatley K, Grey R, Mortality in relation to smoking: Forty years observation Br Med J 1994:309;937

19. Mackay JL, Crofton J. Tobacco and developing world Br Med Bull 1996:52;206

20. Charlton A, Children and smoking: The family circle. Br Med Bull 1996:52;90

21. Russell MAH. The smoking habit and its classification. Practitioner 1974:212;791

22. Waller RE, Froggatt P. Product modification. Br Med Bull 1996:52;193
23. Bonita R, Scragg R, Stewart A, Jackson R, Beaglehole R. Cigarette smoking and risk of premature stroke in men and women. *Br Med J* 1986; 293: 6.

24. Laing SP. The prevalence of cigarette smoking in patients with peripheral arterial disease. In: Greenhalgh RM, ed. *Smoking in Arterial Diseases*. Longon: Pitman Medical, 1981: 9.

25. Somerville KW, Logan RFA, Edmund M, Langman MJS. Smoking and Crohn’s disease. *Br Med J* 1984; 289: 954

26. Clarke A, Morgan R, Newman A. Smoking as a risk factor in cancer of the cervix: additional evidence from a case control study. *Am J Epidemiol* 1982; 10;59

27. Ramakrishan S, Sulochana KN, Selvaraj T *et al*. Smoking of beedes and cataract: cadmium and vitamin C in the lens and blood. *Br J Ophthalmol* 1995; 79: 202

28. Hopper JL, Seeman E. The bone density of female twins discordant for tobacco use. *N Engl J Med* 1994; 330: 387.

29. O’Doherty CJ, Macintyre C. Palmoplantar pustulosis and smoking. *Br Med J* 1985; 291

30. Surgeon General. *The Health Consequences of Smoking: the Changing Cigarette*. Washington, DC: US Department of Health and Human Services, 1981
31. Buchan PC. Cigarette smoking in pregnancy and foetal hyperviscosity. *Br Med J* 1983; 286:131

32. Anderson HR, Cook DG. Passive smoking and sudden infant death syndrome: review of the epidemiological evidence. *Thorax* 1997; 52: 1003

33. Trichopoulos D, Kalandidi A, Sparros L, MacMahon B. Lung cancer and passive smoking. *Int J Cancer* 1981; 27: 1

34. Hirayama T. Non-smoking wives of heavy smokers have a higher risk of lung cancer: study from Japan. *Br Med J* 1971; 1: 183

35. Bjartveit K, Lochson PM, Aaro LE. Controlling the epidemic: legislation and restrictive measures. *Can J Public Health* 1981; 72:

36. Harrisons principle of Internal medicine 18e Mc Graw Hill,2012,p2151-2159

37. Gregg L. Ruppel. Manual of Pulmonary function Testing , 9e,Mosby Elsevier,2009;p 36-89

38. Hunninghake GM et al: MMP12, lung function, and COPD in high-risk populations. *N Engl J Med* 361:2599, 2009

39. Buffels J, Degryse J, Heyrman J, Decramer M. Office spirometry significantly improves early detection of COPD in general practice. *Chest* 2004;125:1394-1399.
| S.NO. | AGE | HEIGHT | WEIGHT | BMI | ONSET | PY | SI | FVCm | FVCp | FEV1m | FEV1p | FEV1/FVCm | FEV1/FVCp | PEF | MEF25-75 | MEF75 | MEF50 | MEF25 |
|-------|-----|--------|--------|-----|-------|----|----|------|------|-------|-------|-----------|----------|-----|---------|-------|-------|-------|
| 1     | 32  | 170    | 60     | 20.8| 20    | 12 | 240| 3.36 | 126  | 3.02  | 78    | 0.6       | 60       | 41 | 43      | 34    | 40    | 83    |
| 2     | 53  | 171    | 56     | 19.2| 23    | 9  | 180| 3.67 | 76   | 2.98  | 84    | 0.78      | 116      | 91 | 114     | 100   | 133   | 123   |
| 3     | 43  | 146    | 45     | 21.1| 23    | 10 | 200| 2.46 | 70   | 2.09  | 54    | 0.66      | 66       | 54 | 48      | 43    | 22    | 12    |
| 4     | 36  | 160    | 58     | 22.7| 23    | 8  | 160| 2.72 | 58   | 1.98  | 79    | 0.72      | 139      | 80 | 113     | 81    | 78    | 247   |
| 5     | 44  | 160    | 60     | 23.4| 20    | 10 | 200| 3.11 | 69   | 2.7   | 78    | 0.84      | 116      | 53 | 76      | 56    | 79    | 109   |
| 6     | 60  | 172    | 65     | 22   | 24    | 36 | 720| 3.85 | 35   | 2.99  | 78    | 0.53      | 72       | 21 | 7       | 7     | 6     | 9     |
| 7     | 33  | 175    | 58     | 18.9| 20    | 6  | 120| 5.09 | 69   | 4.31  | 82    | 0.83      | 121      | 68 | 86      | 75    | 83    | 111   |
| 8     | 43  | 160    | 62     | 24.2| 21    | 12.5| 230| 3.33 | 75   | 2.9   | 79    | 0.84      | 109      | 60 | 69      | 63    | 70    | 78    |
| 9     | 39  | 165    | 45     | 16.5| 20    | 8  | 160| 2.52 | 73   | 2.15  | 69    | 0.82      | 99       | 73 | 50      | 74    | 80    | 84    |
| 10    | 54  | 148    | 55     | 25.1| 16    | 7.2| 144| 2.78 | 70   | 2.31  | 58    | 0.77      | 89       | 49 | 25      | 44    | 31    | 24     |
| 11    | 50  | 160    | 50     | 19.5| 18    | 7.5| 150| 3.58 | 106  | 2.94  | 100   | 0.78      | 99       | 37 | 18      | 18    | 24    | 35     |
| 12    | 44  | 165    | 55     | 27.1| 19    | 10 | 200| 4.02 | 82   | 3.33  | 80    | 0.79      | 101      | 112| 57      | 84    | 61    | 59     |
| 13    | 43  | 160    | 55     | 25.4| 24    | 11.5| 230| 3.11 | 76   | 2.7   | 78    | 0.84      | 106      | 102| 73      | 83    | 79    | 67     |
| 14    | 38  | 154    | 60     | 25.3| 20    | 5  | 102| 3.28 | 83   | 2.86  | 72    | 0.84      | 89       | 64 | 41      | 66    | 46    | 35     |
| 15    | 41  | 159    | 57     | 22.5| 21    | 11.5| 230| 3.5  | 86   | 3.05  | 63    | 0.69      | 69       | 38 | 33      | 42    | 33    | 27     |
| 16    | 59  | 160    | 63     | 24.6| 18    | 20 | 400| 3.44 | 55   | 2.99  | 65    | 0.67      | 67       | 31 | 9       | 28    | 16    | 5      |
| 17    | 53  | 175    | 65     | 21.2| 19    | 9  | 180| 4.36 | 89   | 3.5   | 93    | 0.78      | 107      | 65 | 90      | 73    | 86    | 110    |
| 18    | 50  | 148    | 50     | 26.5| 23    | 5  | 100| 2.88 | 74   | 2.42  | 86    | 0.78      | 125      | 68 | 82      | 74    | 85    | 137    |
| 19    | 42  | 158    | 60     | 22   | 25    | 10 | 200| 2.57 | 87   | 2.2   | 73    | 0.81      | 89       | 76 | 33      | 61    | 39    | 26     |
| 20    | 65  | 148    | 45     | 20.5| 22    | 20 | 400| 1.99 | 69   | 1.62  | 84    | 0.77      | 130      | 72 | 99      | 70    | 98    | 128    |
| 21    | 43  | 160    | 57     | 22.3| 25    | 11.5| 230| 3.65 | 95   | 3.23  | 79    | 0.83      | 89       | 71 | 44      | 58    | 52    | 51     |
| 22    | 33  | 157    | 55     | 21.5| 20    | 4.8 | 96 | 2.97 | 78   | 2.58  | 68    | 0.84      | 90       | 38 | 41      | 37    | 47    | 27     |
| 23    | 45  | 160    | 52     | 20.3| 17    | 13 | 260| 1.58 | 155  | 1.25  | 152   | 0.75      | 104      | 25 | 21      | 19    | 81    | 122    |
| 24    | 50  | 163    | 54     | 20.3| 19    | 18 | 320| 3.65 | 74   | 3.19  | 51    | 0.69      | 69       | 36 | 27      | 33    | 29    | 89     |
| 25    | 34  | 158    | 54     | 21.6| 18    | 8.5| 170| 3.02 | 83   | 2.62  | 83    | 0.84      | 103      | 83 | 75      | 88    | 86    | 60     |
|   |   |   | 70 | 31.1 | 17 | 10 | 200 | 2.66 | 69 | 2.77 | 81 | 0.81 | 122 | 109 | 106 | 110 | 107 | 144 |
|---|---|---|----|------|----|----|-----|------|----|------|----|------|-----|-----|-----|-----|-----|-----|
| 27 | 38 | 168 | 64 | 22.7 | 18 | 15 | 315 | 4.35 | 76 | 3.63 | 54 | 0.68 | 68 | 40 | 24 | 34 | 37 | 29 |
| 28 | 33 | 160 | 59 | 23 | 17 | 17 | 340 | 2.9 | 71 | 2.5 | 60 | 0.68 | 68 | 26 | 30 | 38 | 35 | 23 |
| 29 | 39 | 168 | 69 | 24.4 | 16 | 10 | 200 | 3.61 | 82 | 3.89 | 82 | 0.82 | 104 | 82 | 81 | 91 | 90 | 72 |
| 30 | 58 | 154 | 56 | 23.6 | 19 | 15.5 | 330 | 3.02 | 69 | 2.45 | 67 | 0.77 | 102 | 47 | 48 | 47 | 49 | 54 |
| 31 | 44 | 173 | 58 | 19.4 | 25 | 13.5 | 270 | 4.48 | 65 | 3.67 | 84 | 0.7 | 70 | 32 | 37 | 34 | 38 | 36 |
| 32 | 35 | 186 | 75 | 21.7 | 17 | 7.5 | 150 | 5.46 | 87 | 4.49 | 54 | 0.81 | 99 | 75 | 78 | 85 | 89 | 57 |
| 33 | 41 | 171 | 61 | 20.9 | 20 | 10 | 200 | 4.44 | 73 | 3.67 | 81 | 0.7 | 70 | 76 | 23 | 47 | 29 | 39 |
| 34 | 53 | 156 | 60 | 24.7 | 21 | 15 | 300 | 3.27 | 73 | 2.68 | 71 | 0.78 | 69 | 93 | 55 | 96 | 81 | 37 |
| 35 | 31 | 169 | 69 | 24.2 | 23 | 13 | 260 | 4.74 | 81 | 4.05 | 75 | 0.83 | 95 | 67 | 58 | 82 | 75 | 46 |
| 36 | 51 | 151 | 60 | 26.3 | 18 | 15 | 300 | 2.47 | 103 | 2.09 | 80 | 0.69 | 70 | 52 | 62 | 75 | 85 | 40 |
| 37 | 51 | 150 | 50 | 22.2 | 21 | 10 | 200 | 2.97 | 67 | 2.48 | 60 | 0.79 | 96 | 61 | 34 | 46 | 60 | 40 |
| 38 | 56 | 155 | 55 | 22.9 | 25 | 17.5 | 350 | 3.13 | 80 | 2.55 | 98 | 0.77 | 130 | 52 | 112 | 52 | 97 | 77 |
| 39 | 56 | 160 | 56 | 21.9 | 21 | 15 | 300 | 3.42 | 89 | 2.77 | 83 | 0.77 | 112 | 54 | 191 | 59 | 93 | 110 |
| 40 | 57 | 157 | 65 | 26.4 | 26 | 15.5 | 310 | 3.11 | 112 | 2.52 | 85 | 0.68 | 68 | 32 | 24 | 30 | 61 | 79 |
| 41 | 60 | 160 | 58 | 22.7 | 25 | 18.5 | 370 | 2.66 | 64 | 2.13 | 80 | 0.7 | 70 | 63 | 49 | 53 | 48 | 48 |
| 42 | 53 | 170 | 65 | 22.5 | 23 | 17.5 | 350 | 2.38 | 100 | 2 | 80 | 0.69 | 69 | 61 | 23 | 48 | 48 | 150 |
| 43 | 37 | 156 | 51 | 21 | 18 | 10 | 200 | 3.68 | 101 | 3.14 | 91 | 0.81 | 96 | 46 | 68 | 45 | 79 | 61 |
| 44 | 44 | 160 | 82 | 32 | 17 | 10 | 200 | 3.73 | 84 | 3.11 | 84 | 0.79 | 105 | 128 | 77 | 137 | 101 | 57 |
| 45 | 45 | 168 | 76 | 26.9 | 24 | 12.5 | 250 | 3.65 | 70 | 2.85 | 80 | 0.7 | 70 | 54 | 25 | 52 | 48 | 49 |
| 46 | 40 | 151 | 56 | 24.6 | 20 | 10 | 200 | 3.02 | 80 | 2.6 | 69 | 0.18 | 91 | 46 | 38 | 39 | 68 | 36 |
| 47 | 36 | 158 | 57 | 22.8 | 20 | 10 | 200 | 3.82 | 81 | 3.26 | 75 | 0.81 | 98 | 66 | 54 | 68 | 66 | 45 |
| 48 | 59 | 162 | 52 | 19.8 | 16 | 20 | 400 | 3.46 | 78 | 2.76 | 97 | 0.76 | 131 | 66 | 121 | 64 | 118 | 47 |
| 49 | 53 | 177 | 60 | 19.2 | 19 | 15 | 300 | 4.22 | 98 | 3.29 | 80 | 0.67 | 67 | 74 | 27 | 56 | 31 | 28 |
| 50 | 36 | 160 | 67 | 26.2 | 23 | 9 | 180 | 3.11 | 82 | 2.7 | 80 | 0.84 | 101 | 79 | 59 | 78 | 63 | 51 |
| 51 | 39 | 163 | 64 | 24.1 | 18 | 10 | 200 | 2.87 | 79 | 2.47 | 79 | 0.81 | 106 | 99 | 80 | 105 | 104 | 59 |
| 52 | 35 | 174 | 60 | 19.8 | 19 | 8 | 160 | 5.03 | 79 | 4.27 | 81 | 0.83 | 105 | 68 | 77 | 72 | 75 | 76 |
| 53 | 45 | 160 | 45 | 17.6 | 19 | 10 | 200 | 3.11 | 79 | 2.7 | 74 | 0.84 | 97 | 93 | 59 | 93 | 75 | 34 |
| 54 | 60 | 156 | 54 | 22.2 | 25 | 17.5 | 350 | 3.09 | 822 | 2.48 | 52 | 0.65 | 65 | 24 | 15 | 22 | 22 | 12 |
| 55 | 38 | 159 | 59 | 23.3 | 25 | 7.2 | 144 | 2.98 | 127 | 2.59 | 109 | 0.84 | 89 | 51 | 19 | 44 | 43 | 66 |
|----|----|-----|----|------|----|-----|-----|------|-----|------|-----|-----|----|----|----|----|----|----|
| 56 | 44 | 161 | 60 | 23.1 | 20 | 11 | 220 | 3.79 | 112 | 3.76 | 109 | 0.79 | 102 | 72 | 88 | 82 | 108 | 89 |
| 57 | 46 | 151 | 68 | 29.8 | 22 | 13.5 | 270 | 2.43 | 130 | 2.04 | 109 | 0.85 | 83 | 85 | 61 | 84 | 74 | 39 |
| 58 | 47 | 160 | 79 | 30.9 | 19 | 13.5 | 270 | 2.53 | 77 | 2.15 | 88 | 0.8 | 121 | 49 | 33 | 70 | 60 | 77 |
| 59 | 35 | 170 | 75 | 26 | 20 | 18 | 360 | 4.82 | 90 | 4.03 | 80 | 0.69 | 69 | 48 | 33 | 47 | 37 | 33 |
| 60 | 60 | 160 | 55 | 21.5 | 17 | 17.5 | 350 | 2.69 | 62 | 2.16 | 78 | 0.76 | 132 | 107 | 158 | 109 | 60 | 62 |
| 61 | 45 | 150 | 54 | 24 | 25 | 12 | 240 | 2.36 | 80 | 2 | 81 | 0.68 | 68 | 55 | 11 | 42 | 23 | 70 |
| 62 | 57 | 160 | 45 | 17.6 | 21 | 17.5 | 350 | 3.39 | 80 | 2.27 | 70 | 0.77 | 91 | 51 | 33 | 56 | 51 | 22 |
| 63 | 42 | 171 | 63 | 21.5 | 22 | 18 | 360 | 2.15 | 81 | 1.8 | 80 | 0.7 | 70 | 44 | 54 | 42 | 32 | 21 |
| 64 | 36 | 172 | 65 | 22 | 18 | 6 | 160 | 3.3 | 67 | 2.92 | 80 | 0.74 | 123 | 83 | 121 | 89 | 102 | 45 |
| 65 | 63 | 175 | 65 | 21.5 | 20 | 11.4 | 228 | 3.84 | 67 | 2.92 | 80 | 0.74 | 102 | 78 | 101 | 81 | 76 | 51 |
| 66 | 39 | 162 | 58 | 22.1 | 25 | 10 | 200 | 3.11 | 83 | 2.7 | 95 | 0.84 | 119 | 76 | 98 | 75 | 96 | 46 |
| 67 | 61 | 171 | 69 | 23.6 | 19 | 20 | 400 | 3.05 | 95 | 2.59 | 84 | 0.77 | 97 | 104 | 56 | 85 | 77 | 29 |
| 68 | 44 | 159 | 57 | 22.5 | 21 | 11 | 220 | 4.05 | 84 | 3.54 | 82 | 0.83 | 103 | 88 | 73 | 97 | 82 | 72 |
| 69 | 49 | 160 | 56 | 21.9 | 22 | 15 | 300 | 2.82 | 116 | 2.1 | 80 | 0.69 | 69 | 54 | 56 | 78 | 70 | 59 |
| 70 | 39 | 169 | 65 | 22.8 | 17 | 15 | 300 | 3.95 | 114 | 3.45 | 81 | 0.69 | 69 | 57 | 61 | 60 | 41 | 39 |
| 71 | 60 | 140 | 58 | 29.6 | 19 | 10.5 | 210 | 2.26 | 64 | 2.13 | 65 | 0.76 | 105 | 63 | 49 | 63 | 60 | 58 |
| 72 | 36 | 175 | 68 | 22.2 | 25 | 9 | 180 | 4.59 | 75 | 3.79 | 77 | 0.85 | 100 | 68 | 70 | 73 | 74 | 69 |
| 73 | 47 | 160 | 62 | 24.2 | 18 | 10 | 200 | 3.54 | 59 | 2.94 | 57 | 0.79 | 103 | 47 | 44 | 46 | 49 | 50 |
| 74 | 44 | 170 | 82 | 28.4 | 22 | 11 | 220 | 3.73 | 84 | 3.11 | 85 | 0.79 | 105 | 128 | 77 | 137 | 101 | 57 |
| 75 | 49 | 166 | 52 | 17.9 | 22 | 10 | 220 | 3.46 | 78 | 2.76 | 97 | 0.76 | 131 | 66 | 131 | 64 | 117 | 77 |
| 76 | 44 | 168 | 60 | 21.3 | 24 | 8.8 | 176 | 3.4 | 70 | 2.83 | 63 | 0.85 | 83 | 68 | 26 | 73 | 46 | 9 |
| 77 | 63 | 177 | 65 | 20.7 | 22 | 20 | 400 | 4.22 | 81 | 3.69 | 80 | 0.66 | 66 | 74 | 57 | 54 | 23 | 7 |
| 78 | 44 | 170 | 67 | 23.2 | 23 | 11 | 220 | 3.11 | 82 | 2.7 | 80 | 0.84 | 101 | 79 | 59 | 78 | 63 | 51 |
| 79 | 39 | 163 | 64 | 24.1 | 22 | 9.5 | 190 | 2.87 | 78 | 2.47 | 79 | 0.82 | 106 | 99 | 80 | 105 | 104 | 59 |
| 80 | 35 | 174 | 60 | 19.8 | 20 | 8.5 | 170 | 5.03 | 79 | 4.27 | 81 | 0.8 | 105 | 68 | 77 | 72 | 75 | 76 |
| 81 | 35 | 160 | 60 | 23.4 | 18 | 8.5 | 170 | 3.11 | 79 | 2.6 | 75 | 0.84 | 97 | 93 | 59 | 93 | 75 | 34 |
| 82 | 40 | 166 | 58 | 21 | 18 | 9.5 | 190 | 3.68 | 66 | 3.21 | 61 | 0.83 | 97 | 57 | 45 | 65 | 46 | 42 |
| 83 | 58 | 160 | 60 | 23.4 | 21 | 22.5 | 450 | 3.09 | 82 | 2.48 | 51 | 0.65 | 65 | 24 | 15 | 22 | 26 | 12 |
| 84 | 46 | 163 | 63 | 23.7 | 18 | 8.8 | 176 | 3.79 | 112 | 3.16 | 109 | 0.79 | 102 | 72 | 88 | 82 | 108 | 89 |
|----|----|-----|----|------|----|-----|-----|------|-----|------|----|------|----|----|----|----|-----|----|
| 85 | 36 | 161 | 70 | 27 | 24 | 9 | 180 | 2.43 | 130 | 2.04 | 109 | 0.85 | 83 | 85 | 61 | 84 | 74 | 39 |
| 86 | 47 | 162 | 70 | 26.7 | 18 | 11 | 220 | 2.53 | 77 | 2.15 | 88 | 0.8 | 121 | 49 | 52 | 42 | 60 | 77 |
| 87 | 52 | 160 | 55 | 21.5 | 25 | 8.1 | 162 | 2.69 | 62 | 2.16 | 78 | 0.76 | 110 | 107 | 150 | 100 | 60 | 46 |
| 88 | 49 | 160 | 56 | 21.9 | 25 | 12 | 240 | 3.11 | 83 | 2.7 | 95 | 0.84 | 119 | 70 | 98 | 75 | 96 | 146 |
| 89 | 51 | 173 | 60 | 20 | 19 | 15 | 300 | 3.05 | 95 | 2.59 | 84 | 0.77 | 97 | 104 | 56 | 85 | 76 | 39 |
| 90 | 38 | 157 | 56 | 22.7 | 21 | 10 | 200 | 4.05 | 85 | 3.5 | 83 | 0.83 | 103 | 88 | 73 | 97 | 82 | 72 |
| 91 | 49 | 160 | 58 | 22.7 | 18 | 10 | 200 | 2 | 68 | 1.65 | 70 | 0.79 | 110 | 35 | 45 | 49 | 42 | 74 |
| 92 | 48 | 165 | 62 | 22.8 | 24 | 7.2 | 144 | 4.22 | 88 | 3.66 | 86 | 0.83 | 115 | 65 | 89 | 71 | 94 | 128 |
| 93 | 48 | 168 | 65 | 23 | 24 | 11.2 | 224 | 2.84 | 64 | 2.42 | 75 | 0.8 | 125 | 68 | 85 | 75 | 80 | 66 |
| 94 | 52 | 155 | 56 | 23.3 | 20 | 13.5 | 270 | 1.66 | 65 | 1.33 | 68 | 0.75 | 94 | 43 | 53 | 39 | 33 | 25 |
| 95 | 61 | 159 | 50 | 21.8 | 25 | 20 | 400 | 2.97 | 110 | 2.29 | 80 | 0.69 | 69 | 99 | 39 | 74 | 43 | 26 |
| 96 | 49 | 166 | 60 | 21.8 | 21 | 12 | 240 | 1.79 | 95 | 1.44 | 100 | 0.76 | 112 | 83 | 62 | 73 | 51 | 84 |
| 97 | 30 | 170 | 68 | 23.5 | 19 | 5 | 100 | 3.3 | 95 | 2.9 | 77 | 0.8 | 84 | 87 | 12 | 70 | 59 | 95 |
| 98 | 49 | 170 | 62 | 21.5 | 20 | 10 | 200 | 2.17 | 81 | 1.8 | 69 | 0.77 | 91 | 76 | 28 | 67 | 36 | 21 |
| 99 | 39 | 166 | 60 | 21.8 | 24 | 9.5 | 190 | 4.2 | 90 | 3.5 | 78 | 0.8 | 88 | 113 | 41 | 78 | 50 | 33 |
| 100 | 55 | 160 | 75 | 29.3 | 20 | 12 | 240 | 2.55 | 74 | 2.15 | 71 | 0.79 | 103 | 62 | 59 | 68 | 77 | 36 |
| 101 | 39 | 169 | 69 | 24.2 | 25 | 9.5 | 190 | 2.96 | 74 | 2.55 | 78 | 0.82 | 110 | 38 | 70 | 28 | 46 | 67 |
| 102 | 45 | 157 | 52 | 21.1 | 20 | 10 | 200 | 3.13 | 104 | 2.65 | 111 | 0.79 | 114 | 85 | 120 | 94 | 130 | 153 |
| 103 | 51 | 148 | 68 | 31 | 20 | 9 | 180 | 2.74 | 103 | 2.22 | 116 | 0.76 | 119 | 120 | 96 | 127 | 33 | 56 |
| 104 | 44 | 164 | 60 | 22.3 | 21 | 7.2 | 144 | 2.79 | 69 | 2.38 | 81 | 0.81 | 124 | 71 | 103 | 79 | 93 | 53 |
| 105 | 35 | 160 | 73 | 28.5 | 20 | 8.5 | 170 | 2.07 | 89 | 2.65 | 89 | 0.82 | 104 | 73 | 81 | 77 | 86 | 73 |
| 106 | 38 | 155 | 56 | 23.3 | 18 | 10 | 200 | 3.6 | 80 | 3.07 | 75 | 0.8 | 99 | 72 | 58 | 79 | 76 | 39 |
| 107 | 51 | 153 | 69 | 28.7 | 18 | 15 | 300 | 2.56 | 80 | 2.17 | 75 | 0.79 | 90 | 59 | 33 | 60 | 40 | 24 |
| 108 | 55 | 168 | 62 | 22 | 21 | 12 | 240 | 1.84 | 109 | 1.5 | 100 | 0.77 | 97 | 87 | 45 | 64 | 54 | 33 |
| 109 | 37 | 162 | 52 | 19.8 | 25 | 10 | 200 | 4.03 | 85 | 3.4 | 73 | 0.81 | 89 | 60 | 41 | 58 | 48 | 36 |
| 110 | 47 | 166 | 51 | 18.5 | 17 | 11 | 220 | 2.9 | 83 | 2.27 | 86 | 0.75 | 108 | 77 | 68 | 83 | 80 | 72 |
| 111 | 59 | 155 | 65 | 27 | 25 | 10.2 | 204 | 2 | 74 | 1.65 | 74 | 0.79 | 106 | 44 | 43 | 47 | 42 | 51 |
| 112 | 58 | 162 | 60 | 22.9 | 25 | 10.2 | 204 | 2.34 | 75 | 1.95 | 77 | 0.79 | 100 | 77 | 44 | 80 | 75 | 43 |
|    |    |    |    |    |    |    |    |    |    |    |    |    |    |
|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| 171|  35| 160|  73| 28.5|  20|  8.5| 170|  4.29|  79| 3.59|  89|  0.8| 105| 110|
| 172|  38| 155|  56|  23.3|  18|  10| 200|  3.11|  77|  2.7|  68|  0.84|  91|  48|
| 173|  51| 153|  49|  20.9|  18|  15| 300|  2.2 |  78|  1.8|  81|  0.79| 112|  61|
| 174|  55| 168|  62|   22|  21|  12| 240|  2.58| 114| 2.21| 118|  0.85| 105| 114|
|    |    |    |    |    |    |    |    |    |    |    |    |    |    |
PROFORMA

NAME:  
AGE:  
SEX:  
STUDY NO.:  
ADDRESS:  
HEIGHT:  
WEIGHT:  
BMI:  
HISTORY:  
AGE OF FIRST SMOKE:  
DURATION:  
SMOKING TYPE: CIGAR/ BEEDIES/CIGARETTES/ETS  
PACK YEARS:  
SMOKING INDEX:  
PRE EXISTING ILLNESS:  
PREMEDICATION:  
PFT:  

| PARAMETER        | TRIAL 1 | TRIAL 2 | TRIAL 3 |
|------------------|---------|---------|---------|
| FVCm             |         |         |         |
| FVCp             |         |         |         |
| FEV1m            |         |         |         |
| FEV1p            |         |         |         |
| FEV1 FVC m       |         |         |         |
| FEV1FVC p        |         |         |         |
| MEF 25- 75       |         |         |         |
| MEF 75           |         |         |         |
| MEF50            |         |         |         |
| MEF 25           |         |         |         |
| PEF              |         |         |         |

GOLD STAGING:  
IMPRESSION:  
ABBREVIATIONS

a1AT – Alpha 1 Antitrypsin
ABG – Arterial Blood Gas
ATS – American Thoracic Society
BMI – Body Mass Index
COPD – Chronic Obstructive Pulmonary Disease
ERS – European Respiratory Society
ERV – Expiratory Reserve Volume
ETS – Environmental Tobacco Smoke
FEV1 – Forced Expiratory Volume in one second
FRC – Functional Residual Capacity
FVC – Forced Vital Capacity
GOLD – Global Initiative for Obstructive Lung Diseases
HHIP – Hedgehog Interacting Protein
IRV – Inspiratory Reserve Volume
LHS – Lung Health Study
MEF – Mid Expiratory Flow
MMP 12 – Matrix Metalloproteinase
PEF – Peak Expiratory Flow
PEFR – Peak Expiratory Flow Rate
RV – Residual Volume
SI – Smoking Index
TLC – Total Lung Capacity
TPM – Total Particulate Matter
TV – Tidal Volume
VC – Vital Capacity
V/Q – Ventilation Perfusion Ratio
WHO – World Health Organization
This is to certify that the project work titled

**Early detection of COPD in asymptomatic smokers using spirometry** proposed by **Dr. Mohana Sundaram**

part of fulfillment of M.D/M.S course in the subject of Medicine for the year 2012-2015 by The Tamilnadu Dr. MGR Medical University has been cleared by the ethics committee.

CHAIRMAN,
Institutional Ethics Committee
K.A.P. Viswanatham Govt. Medical College, Tiruchirapalli -1
EARLY DETECTION OF COPD IN ASYMPTOMATIC SMOKERS USING SPIROMETRY

Dissertation submitted to
The Tamil Nadu Dr. M.G.R. Medical University
In partial fulfillment of the regulations for
The award of the degree of
M.D. General Medicine [Branch- I],
K.A.P. Viswanatham Government Medical College
& M.G.M. Government Hospital,
Tiruchirapalli

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