EVALUATION OF NUTRTIONAL STATUS IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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CERTIFICATE

This is to certify that the dissertation entitled "**EVALUATION OF NUTRITIONAL STATUS IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE**" is a bonafide work done by **Dr. JAYCHANDRAN R.,** at Madras Medical College, Chennai in partial fulfillment of the university rules and regulations for award of M.D., Degree in General Medicine (Branch-I) under my guidance and supervision during the academic year 2006-2009.

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DECLARATION

I solemnly declare that this dissertation entitled "**EVALUATION OF NUTRITIONAL STATUS IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE**" was done by me at Madras Medical College and Government General Hospital, during 2006-2009 under the guidance and supervision of **Prof. M. JUBILEE, 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 in General Medicine (Branch-I).

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CONTENTS

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of chronic morbidity and mortality throughout the world. It is a preventable and treatable disease with some significant extra pulmonary effects that may contribute to severity in individual patients[1]. It is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal response of the lung to noxious particles or gases.

Nutritional depletion is a prevalent finding in patients who have COPD. Several studies have demonstrated that under nutrition is an independent predictor of all cause and respiratory morbidity and mortality in COPD and has an additive effect with other factors that increase mortality. Investigators have identified a positive correlation between body weight and the Forced Expiratory Volume in the 1st second[2,3]. Even among stable COPD patients there is a high proportion of under nutrition[4]. COPD patients are at risk of weight loss and nutritional deficiencies because of a 15 to 25% increase in resting energy expenditure from breathing; a higher energy cost of daily activities; reduced caloric intake

relative to need because of dyspnea; and the catabolic effect of inflammatory cytokines such as TNF-α[5].

At the same time, excessive weight gain must be avoided as excessive body weight can lead to a decreased pulmonary reserve.

The exact prevalence of malnutrition in COPD is currently unknown because there is no diagnostic method that serves as a reference and no widely accepted definition.

Various biochemical parameters that reflect the level of visceral protein in the body have also been used in assessing the severity of malnutrition.

The present study attempts to determine if there is an association between the degree of malnutrition and severity of airflow obstruction.

OBJECTIVES OF THE STUDY

1. To determine whether Chronic Obstructive Pulmonary Disease is associated with malnutrition.

2. To determine whether there is a relation between the degree of malnutrition and severity of airflow obstruction.

3. To determine whether the severity of airflow obstruction correlates with biochemical markers of visceral protein stores (Serum albumin and Serum prealbumin).

REVIEW OF LITERATURE

Chronic Obstructive Pulmonary Disease is a major cause of chronic morbidity and mortality throughout the world. Many people suffer from this disease for years and die prematurely from it or its complications. COPD is the fourth leading cause of death in the world[6], and further increases in its prevalence and mortality can be predicted in the coming decades[7].

Definition: According to Global initiative for chronic obstructive lung disease (GOLD[1]), COPD is a preventable and treatable disease with some significant extra pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases[1]. The term "emphysema" and "chronic bronchitis", are not included in this definition. Emphysema, or destruction of the gas exchanging surfaces of the lung (alveoli), is a pathological term that is often (but incorrectly) used clinically and describes only one of several structural abnormalities present in patients with COPD[1]. Chronic bronchitis, or the presence of cough and sputum production for at least 3 months in each of two

consecutive years, remains a clinically and epidemiologically useful term[1].

Worldwide, cigarette smoking is the most commonly encountered risk factor for COPD, although in many countries, air pollution resulting from the burning of wood and other biomass fuels has also been identified as a COPD risk factor[1].

The chronic airflow limitation characteristic of COPD is caused by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person[1].

Mechanisms Underlying Airflow Limitation in COPD

INFLAMMATION

Small airway disease	Parenchymal destruction
Loss of alveolar attachments	Airway inflammation
Airway remodeling	Decrease of elastic recoil

AIRFLOW LIMITATION

SPIROMETRIC CLASSIFICATION OF SEVERITY

Spirometry is essential for diagnosis and provides a useful description of the severity of pathological changes in COPD. Spirometry should be performed after the administration of an adequate dose of an inhaled bronchodilator (e.g. 400 mcg salbutamol) in order to minimize variability[8].

Spirometric Classification of COPD **Severity Based on Post-Bronchodilator FEV_1[1]**	
Stage I : Mild	$FEV_1/FVC < 0.70$ FEV1 $\geq$80% predicted
Stage II : Moderate	$FEV_1/FVC < 0.70$ $50\% \leq FEV_1 < 80\%$ predicted
Stage III : Severe	$FEV_1/FVC < 0.70$ $30\% \leq FEV_1 < 50\%$ predicted
Stage IV : Very Severe	$FEV_1/FVC < 0.70$ $FEV_1 < 30\%$ predicted or FEV_1 50% Predicted plus chronic respiratory failure.

SYMPTOMS OF COPD

The characteristic symptoms of COPD are chronic and progressive dyspnea, cough and sputum production. Chronic cough and sputum production may precede the development of airflow limitation by many years. Conversely, significant airflow limitation may develop without chronic cough and sputum production.

STAGES OF COPD

Stage I: Mild COPD – Characterized by mild airflow limitation ($FEV_1/FVC < 0.70$; $FEV_1 \geq 80\%$ predicted). Symptoms of chronic cough and sputum production may be present, but not always[1].

Stage II: Moderate COPD – Characterized by worsening airflow limitation ($FEV_1/FVC < 0.70$; $50\% \leq FEV_1 < 80\%$ predicted), with shortness of breath typically developing on exertion and cough and sputum production sometimes also present[1].

Stage III: Severe COPD – Characterized by further worsening of airflow limitation ($FEV_1/FVC < 0.70$; $30\% \leq FEV_1 < 50\%$ predicted), greater shortness of breath, reduced exercise capacity, fatigue, and

repeated exacerbations that almost always have an impact on patients' quality of life[1].

Stage IV: Very Severe COPD - Characterized by severe airflow limitation (FEV_1/FVC <0.70; FEV_1 <30% predicted *or* FEV_1 <50% predicted plus the presence of chronic respiratory failure or cor pulmonale). Respiratory failure is defined as arterial partial pressure of oxygen (PaO_2) less than 8.0 kPa (60 mm Hg) with or without arterial partial pressure of CO_2 ($PaCO_2$) greater than 6.7 kPa (50 mm Hg) while breathing air at sea level. Respiratory failure may also lead to effects on the heart such as cor pulmonale (right heart failure). At this stage, quality of life is very appreciably impaired and exacerbations may be life threatening[1].

EPIDEMIOLOGY

COPD is underdiagnosed and undertreated, resulting in underestimation of the burden of this disease[9]. The prevalence of COPD is highest in countries where cigarette smoking, for example, is still very common[10]. Prevalence data based on the presence of airflow limitation provide an accurate estimate of the burden of clinically significant COPD[7].

Two large epidemiologic studies, in which the diagnosis of COPD was established using spirometry, evaluated COPD prevalence in 2005. In a nationwide Korean survey involving 9,243 subjects, Kim and colleagues reported that the prevalence of COPD, determined by criteria of the GOLD, was 17.2% among subjects older than 45 years[11]. Prevalence increased with increasing age, especially in males, in those with more than 20 pack-years of smoking, and in low-income subjects. Most of the COPD found was mild to moderate (FEV_1 >50%). Menezes and colleagues reported wide variability in COPD prevalence between five major cities in Latin America[12].

RISK FACTORS FOR COPD

1) Genes: polygenic and hereditary deficiency of alpha-I antitrypsin[13].
2) Exposure to particles
    - Tobacco smoke[14,15].
    - Occupational dusts, organic and inorganic[16-19]
    - Indoor air pollution from heating and cooking with biomass in poorly vented dwellings[20,21].
    - Outdoor air pollution.

3) Decreased Lung growth and development[22].

4) Oxidative stress.

5) Gender: prevalence is more in males compared to females. However in developed countries prevalence is almost equal[23,24].

6) Age: prevalence increases with increase in age[23].

7) Respiratory infections[23].

8) Socioeconomic status: risk of COPD is inversely related to socioeconomic status[25].

9) Nutrition[1-3]

10) Co morbidities[1]

PATHOLOGICAL CHANGES

Proximal airways – *Inflammatory cells:* Macrophages and CD8+ T cells.

Structural changes: Goblet cells, enlarged submucosal glands and squamous metaplasia of epithelium[26].

Peripheral airways – *Inflammatory cells:* Macrophages, T lymphocytes (CD8+ > CD4+), B lymphocytes and fibroblasts.

Structural changes: Airway wall thickening, peribronchial fibrosis, luminal inflammatory exudates and airway narrowing[27].

Lung parenchyma – *Inflammatory cells:* Macrophages, CD8+ T lymphocytes.

Structural changes: Alveolar wall destruction, apoptosis of epithelial and endothelial cells, Centrilobular and Panacinar emphysema[28].

Pulmonary vasculature – *Inflammatory cells:* Macrophages, T lymphocytes.

Structural changes: pulmonary hypertension[29].

PATHOGENESIS

Amplification of the normal inflammatory response of the respiratory tract to chronic irritants appears to be seen in COPD.

Inflammatory Cells: COPD is characterized by recruitment of neutrophils, macrophages and lymphocytes[30]. These cells release

inflammatory mediators and interact with structural cells in the airways and lung parenchyma.

Inflammatory Mediators: Chemotactic factors like leukotriene B_4 and interleukin-8, Proinflammatory cytokines like TNF-alpha, IL-1beta, and IL-6 and Growth factor TGF-β which are released from the inflammatory cells are responsible for inflammation[31].

Oxidative Stress: Oxidative stress may be an important amplifying mechanism in COPD[32]. Oxidants are generated by cigarette smoke and other inhaled particulates and released from activated inflammatory cells. Oxidative stress has several adverse consequences in the lungs, including activation of inflammatory genes, inactivation of antiproteases, stimulation of mucus secretion and stimulation of increased plasma exudation.

Protease-Antiprotease Imbalance: There is compelling evidence for an imbalance in the lungs of COPD patients between proteases and antiproteases[1,13]. There is increase in proteases such as Neutrophil elastase, Cathepsin G, Proteinase 3, Cathepsins B, K, L, S and matrix metalloproteinases like MMP-8, MMP-9 and MMP-12. This is associated with decrease in antiproteinases like alpha-1 antitrypsin,

alpha-1 antichymotrypsin, Elafin, Cystatins and Tissue inhibitors of MMP 1-4.

PATHOPHYSIOLOGY

1. Airflow Limitation and Air Trapping: The peripheral airway obstruction due to inflammation, fibrosis and luminal exudates leads to progressive air trapping during expiration resulting in hyperinflation. Hyperinflation increases functional residual capacity which results in dyspnea and limitation of exercise capacity.

2. Gas Exchange Abnormalities: It results in hypoxemia and hypercapnia.

3. Mucus Hypersecretion: It is due to mucosal metaplasia with increased numbers of goblet cells in response to chronic airway irritation resulting in chronic productive cough.

4. Pulmonary Hypertension: This may develop late in the course of COPD and is due to hypoxic vasoconstriction and structural changes in small pulmonary arteries[33].

PREDICTORS OF MORTALITY IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is a major cause of morbidity and mortality in adults and is currently the fourth leading cause of death in the world[6]. COPD is the only leading cause of death showing increases in prevalence worldwide[34]. Although COPD is characterized primarily by the presence of airflow limitation owing to chronic bronchitis, emphysema, or both, a myriad of systemic manifestations that accompany this disease effectively can signal an increased risk for mortality. Recognizing these manifestations, provides a more comprehensive assessment of disease severity and helps elucidate prognosis.

a) Forced Expiratory Volume in 1 second (FEV_1):

The landmark study of Fletcher and Peto[35] published in 1976, identified a relationship between airflow obstruction and survival in a study of over 2700 British men, followed for 20 – 25 years. These findings were expanded by Anthonisen and colleagues[36] during the Intermittent Positive Pressure Breathing Trial (IPPB), which identifies both age and FEV_1 as independent and accurate predictors of mortality.

b) Airway Hyper-responsiveness (AHR):

The importance of airway hyper-responsiveness (AHR) in obstructive lung diseases is defined better for asthma than for COPD. In a mortality assessment of a cohort of 2000 patients followed over 20 years, Hospers and Colleagues found that increased AHR predicted mortality for COPD after adjusting for gender, age, smoking history and numerous confounders[37]. However, more studies are needed to better define this relationship.

c) Dyspnea

Dyspnea is the cardinal symptom of COPD[38] and the primary reason for seeking medical attention[39,40]. Numerous studies have identified dyspnea as an independent predictor of mortality in COPD. In a prospective, multi-center, 5 year trial, dyspnea was measured by the Medical Research Council Dyspnea Scale in a cohort of 227 patients who had COPD. The survival rate was predicted by the degrees of dyspnea irrespective of the severity of COPD by FEV_1[41].

d) Hypoxemia

The presence of hypoxemia (PaO_2 <55 mmHg or SaO_2 <88%) while the patient is breathing room air is known to predict mortality. Neff and

Petty first published a 30% to 40% reduction in mortality in COPD patients given continuous oxygen[42].

e) Hypercapnia

Presence of chronic hypercapnia is associated with negative prognostic value for survival in COPD[43,44].

f) Static Hyperinflation

In a prospective study, hyperinflation expressed as residual volume/total lung capacity proved to be a powerful predictor of mortality[45].

g) Pulmonary Hypertension

It is defined as a pulmonary artery mean pressure at rest, equal to or greater than 20 mmHg at rest. Increased mortality rate was found in patients with severe pulmonary hypertension, irrespective of level of airflow obstruction[46,47].

h) Malnutrition

Nutritional depletion is a prevalent finding among patients who have COPD, in particular those who have advanced disease. The prevalence of weight loss in stable COPD is in the range of 20%, and it increases to 35% among those who are hospitalized[48,49]. Several studies

have found that the body mass index (BMI) is an independent risk factor for COPD mortality[3,50]. Landbo and colleagues[2], in The Copenhagen City Heart Study, found BMI to be an independent predictor of all-cause and respiratory mortality among COPD patients with FEV_1 less than 50% predicted. The impact of weight change on survival in COPD also was examined retrospectively by Schols and colleagues[51] in 400 COPD patients who participated in a pulmonary rehabilitation programme. A low BMI (less than 25 kg/m^2) was associated with a significant increase in the risk for mortality ($P < .001$). In a prospective post hoc analysis of 203 COPD patients who received nutritional support, weight gain (greater than 2 Kg/8 wks) was a significant predictor of survival[51]. Studies using more complex tests to evaluate nutrition, such as midthigh[52] and midarm[53] muscle cross-sectional area obtained by CT also have shown significant association between malnutrition and mortality in COPD, with a predictive value that is superior to that of BMI. Taken together, the evidence suggests that weight loss can be considered an independent risk factor for mortality in patients who have COPD.

i) Exercise capacity:

Exercise intolerance affects many patients who have COPD[54]. The 6 minute walk distance test is a simple field test that has been correlated with mortality[55].

j) Anemia

Anemia is a common comorbidity in many chronic diseases and its importance in COPD is gaining interest. Recent reports suggests that anemia in patients who have COPD may be more prevalent than expected and related to mortality[56].

MULTIDIMENSIONAL MORTALITY RISK ASSESSMENT IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

For many years, FEV_1 and age were considered the most important prognostic indicators of COPD. Unfortunately, both of them are, for most part, irreversible. Recent evidence shows that multiple factors, other than FEV_1 can predict mortality in this disease, as discussed earlier. These factors are reflections of the systemic involvement of COPD and many of them are amenable to treatment. In a pioneer study by Celli and colleagues[57], 207 patients who had COPD were enrolled prospectively and the predictive value of numerous variables was evaluated. The authors identified four variables that predicted an elevated risk for death. BMI (B), degree of airflow obstruction (O) as measured by FEV_1, dyspnea as measured by the MRC dyspnea scale (D) and excercise capacity as measured by 6 metre walk test (E). These variables were incorporated into a multidimensional scale, the BODE index, that ranged from 0 (least

risk) to 10 (highest risk). The authors found that each quartile increase in the BODE index score yielded an increase in the risk for mortality.

Calculation of the BODE Index

BODE score				
Variable	0	1	2	3
FEV_1 % predicted	≥65	50 – 65	35 – 49	≤35
Dyspnea: MRC	0 – 1	2	3	4
6MWD meters	≥350	250 – 349	150 – 249	≤149
BMI	>21	≤21	-	-

FEV_1 - Forced Expiratory volume in the first second

6MWD – Six Meter Walk Distance

MRC – Medical Research Council

BMI – Body Mass Index

MALNUTRITION IN COPD

The effect of nutritional data on respiratory muscle function is controversial. It is postulated that under-nutrition plays an additive role in the variation of weakness of respiratory muscles in COPD.

Studies on re-nutrition in COPD showed an improvement in muscle strength suggesting that malnutrition is an important cause of diminished muscle strength[58].

A substantial proportion of patients with COPD are found to be malnourished. The incidence depends largely on disease severity. Some studies have shown that about 25 percent of patients with COPD suffer from under-nutrition[59]. Those with FEV_1 <35%, it is found to be 50%. Even patients with a moderate airflow obstruction may have an incidence up to 25%[60]. Poor nutritional status may adversely affect respiratory function in COPD patients.

THE EFFECTS OF MALNUTRTION ON THE RESPIRATORY APPARATUS:

– *Changes in the respiratory musculature*. Abnormalities in skeletal muscle are common in COPD patients; contractility, strength, and

resistance are reduced, while fatigability increases[61]. The etiology of muscular dysfunction in COPD is multifactorial and includes electrolyte abnormalities, atrophy due to lack of exercise, prolonged use of drugs such as corticosteroids[62,63], changes in the geometry of the thoracic cage, hypoxia, and malnutrition. Malnutrition decreases muscular strength and resistance, and reduces glycolytic and oxidative capacity in both type I and type II fibers. A weak respiratory musculature contributes to dyspnea and has a negative impact on exercise tolerance[64].

– *Morphological changes*. In various animal models, the lungs have been shown to lose mass as a result of malnutrition, although to a lesser extent than the body as a whole. This loss primarily affects protein content but fat content also diminishes. From a morphological standpoint this leads to a greater tendency of the lung to collapse, elongation of the airspaces, destruction of septa, and thinning of the interalveolar walls. These changes are due to an increase in proteolytic activity and a decrease in collagen content and may be partially reversible if the patient is adequately renourished[65,66].

– *Biochemical changes*. Biochemical changes affect the alveolar surfactant provoking a decrease in total phospholipids, phosphatidylglycerol, and phosphatidylcholine. This triggers a rise in surface tension and a

corresponding decrease in the protective effectiveness of the surfactant. These changes are due to a reduction in the enzyme activity that regulates its synthesis, to a reduced availability of energy substrates, and to characteristics of the local oxidative metabolism. These abnormalities may be reversible on re-nourishment, and a normal state is recovered more rapidly than in the case of connective tissue[67].

In summary (although much remains to be clarified and most of the studies in the literature have used animal models), malnutrition appears to cause a series of alterations in muscles, especially the diaphragm, and also affects the lung parenchyma. The lungs become emphysematous in appearance and this changes respiratory dynamics.

EFFECT OF RENUTRITION

Nutritional repletion can improve respiratory muscle strength in some patients. When 6 ambulatory patients with COPD were given oral nutritional repletion for two weeks, baby weight increased by six percent and transdiaphragmatic pressure increased by 41 percent[58].

The mechanisms of improved muscle performance with re-nutrition are not clear. In animal and human studies, chronic hypocaloric dieting produced changes in skeletal muscle that may be important in the genesis of muscle dysfunction. These changes include protein catabolism,

depletion of glycolytic and oxidative enzymes, reduction in high energy phosphate stores, increases in intracellular calcium.

NUTRITIONAL ASSESSMENT IN PATIENTS WITH COPD

In general, insufficient attention is paid to the nutritional assessment of patients with COPD in routine practice. It should, like spirometry and arterial blood gas analysis, be included in the initial clinical evaluation of these patients. Regular follow-up of nutritional status is also essential because this variable has been shown to have independent prognostic value, a more than sufficient reason for its assessment[68]. Consequently, simple, easy-to-use, cheap, and reproducible procedures for the assessment of nutritional status are needed.

There is no single ideal nutritional marker, but a combination of several simple parameters can facilitate the diagnosis of malnutrition in these patients[69]. Several parameters are used to assess nutritional status and they can be basically categorized as either anthropometric or biochemical.

– Body weight, which is very easy to measure. A record of weight over time is more useful than a single isolated measurement.

– Comparison with the predicted weight for height and sex in a specific population expressed as ideal body weight, or calculation of BMI. These variables are easily calculated. The BMI has been shown to correlate well with lung function parameters, such as the diffusing capacity of the lung for carbon monoxide, FEV1, and the ratio of FEV1 to forced vital capacity.

– Assessment of the muscle compartment using anthropometric data or densitometry.

– Evaluation of body composition by measurement of skinfolds or, even better, bioelectrical impedance analysis. Body composition, and in particular the fat-free mass index, has been shown to be an independent predictor of mortality in COPD[70].

– Biochemical markers, such as albumin, prealbumin, albumin and transferrin. These will very often vary due to non-nutritional factors such as liver disease, cardiac failure, long term steroid therapy, etc[69].

MEASURES OF VISCERAL PROTEIN STORES

Serum protein levels are important markers of the body protein pool. Measurable proteins include albumin, transferrin, transthyretin (prealbumin), retinol-binding protein (RBP), fibronectin, C-reactive protein, interleukins, and others. Proteins with a long half-life are most useful in evaluating chronic nutritional changes in the outpatient setting. Proteins with a short half-life are most useful in the acute or subacute settings.

Albumin

Serum albumin levels have long been considered a major measure of malnutrition and the defining value for determining the diagnosis of kwashiorkor. Albumin levels are highly predictive of mortality in the hospital[71] and mortality in the general population[72]. For every 2.5 g/L decrease in serum albumin concentration, there is a 24% to 56% increase in the likelihood of dying[71].

Albumin has a long half-life of approximately 18 days[73]. Serum levels of albumin reflect the net result of hepatic synthesis (12–15 g/d), plasma distribution, and protein loss.

Serum albumin levels often decline rapidly after hospital admission[74]. The rate of fall is too rapid to allow for a nutritional explanation. Two reasons appear to explain this fall: postural changes and cytokines. Altering posture from the upright to the recumbent position produces a decline in serum albumin of 5 g/L. Cytokines such as tumor necrosis factor-α, interleukin-2 (IL-2), and IL-6 inhibit albumin production by inhibiting albumin gene expression and cause a vascular endothelial leak, resulting in an increase plasma clearance rate of albumin[75]. Chronic alteration in serum albumin can occur with diseases affecting hepatic production of albumin (liver disease and congestive heart failure) or the rate of albumin loss (nephrotic syndrome and protein-losing enteropathies). Thus, although serum albumin levels remained the gold standard for the diagnosis of protein energy malnutrition, they are a somewhat tarnished standard.

Several studies have shown a correlation between low serum albumin and the severity of airway obstruction[76]. Katsura et al found that low albumin levels can be a risk factor for poor outcome in the disease[77].

Prealbumin

Prealbumin, also known as transthyretin, is a transport protein for thyroxine. Prealbumin is popularized by its short half-life and superior

sensitivity in evaluating acute nutritional change[78]. Because of their long half-lives, downward changes of the concentrations of albumin and transferrin are not seen until prolonged or severe malnutrition is present[78-80]. The long half-lives also prevent the detection of short-term responses to nutritional support. Prealbumin levels decrease faster than do levels of albumin and transferrin in cases of protein depletion[81] and returns to normal after nutritional repletion[82]. Among nursing-home residents who were hospitalized, severe hypoprealbuminemia predicted extended hospitalization but not mortality[83]. In cancer patients receiving total parenteral nutrition, plasma levels of prealbumin rapidly increased in patients who survived and rapidly fell in patients who did not[84]. Winkler et al. showed that, after 1 wk of adequate feeding of malnourished patients, only 36% had serum albumin within normal values compared with transferrin (80%)and prealbumin (98%)[85]. If prealbumin fails to increase despite 10 to 14 d of adequate parenteral nutrition, it indicates a poor prognosis for short-term survival in cancer patients[85]. Low serum prealbumin levels were predictive of death and indicative of sepsis in burn patients[86]. Severely low levels of prealbumin have been shown to increase in-hospital stay of nursing-home patients when admitted to the hospital[83]. Prealbumin is a stable and symmetrical tetramer composed of four identical subunits[87]. It is normally bound to the retinol-binding protein (RBP) at a 1:1 molar ratio in physiologic pH 6. In addition to thyroxin

transport, prealbumin plays a role in vitamin A transportation via this complex. Prealbumin has the highest proportion of essential to non-essential amino acids of any protein in the body. It is rich in tryptophan, which plays a major role in the initiation of protein synthesis. Prealbumin has a small pool and a half-life of 2 d[88]. PA levels can be affected by factors other than malnutrition. Prealbumin has been noted to be lower in women than in men in the same age group[89,90]. Although aging does not affect prealbumin levels in healthy individuals, it seems that a decrease in prealbumin levels may occur in very old men (>90 y), so that their values fall to within the same range as those in women[89]. Decreased prealbumin levels are seen in end-stage liver disease (presumably due to decrease production)[91], inflammation[92], stress[93], and iron deficiency[94]. Renal insufficiency and steroid use each causes an increase in serum prealbumin levels[95].

Because of its unique characteristics and its small pool size, prealbumin is a better and more sensitive indicator of acute changes in protein status in both young and old.

Studies done on COPD patients have shown that prealbumin levels are related to level of airway function. However, all the prealbumin values fell within the normal range[96].

MATERIALS AND METHODS

SETTINGS

Out patient clinics at

- Department of Thoracic Medicine

  Madras Medical College and Government General Hospital

  Chennai – 600 003

- Institute of Thoracic Medicine

  Chetpet

  Chennai

ETHICAL COMMITTEE APPROVAL

Obtained

STUDY DESIGN

Cross sectional study design

PERIOD OF STUDY

June 2007 to September 2008

SAMPLE SIZE

50 cases

CONSENT

Informed consent was obtained from all patients participating in the study

INCLUSION CRITERIA

1. Patients diagnosed to have Chronic Obstructive Pulmonary Diseases as per GOLD criteria
2. Patients in the age group 40 – 60 years
3. Patients on treatment for less than one year
4. Patients not on corticosteroid

EXCLUSION CRITERIA

1. Patients with exacerbation of symptoms <2 months prior to study
2. Patients with cor pulmonale
3. Patients with diabetes mellitus
4. Critically ill patients
5. Female patients
6. Patients with pulmonary tuberculosis
7. Patients who are unable to perform spirometry

8. Patients with bronchial asthma, bronchiectasis, cystic fibrosis, upper airway obstruction.
9. Patients with concomitant diseases that may alter nutritional status e.g. heart failure, liver cirrhosis, uncontrolled diabetes
10. Non smokers

METHODOLOGY

Out of 102 patients initially enrolled for the study, 50 patients were selected. Others were excluded as per exclusion criteria.

The patients were defined as having COPD based on GOLD criteria with spirometry showing, post bronchodilator FEV_1 / FVC ratio <0.70.

The analysis was restricted to patients in the age group of 40 – 60 years. All the patients chosen were smokers and all the patients were males. This was done to ensure uniformity of analysis (standards for variation of prealbumin between various age groups and gender are not available).

For each subject, medical history was obtained and clinical examination was done. All subjects had a baseline blood sugar value and renal function tests. On the study day, height and weight were measured.

Weight was measured to the nearest 100 g. Height was measured to the nearest mm using a stadiometer. Body Mass Index (BMI) was calculated using the formula:

$$BMI = \text{Weight (kg)} / \text{Height (m)}^2$$

TRICEPS SKINFOLD THICKNESS (TSF)

Triceps skinfold thickness was measured in all subjects in the non dominant arm using a standard Vernier calipers[97]. Measurement was taken mid way between the acromion and olecranon process and was measured to the nearest 0.1 mm. Most population studies show an average value of 1.5 ± 0.6 cm[98].

MIDARM CIRCUMFERENCE (MAC)

Midarm circumference of the non-dominant arm was measured using a standard measuring tape. The measurement was done mid way between the olecranon process and acromion process and taken to the nearest mm[99].

Nutritional indices were calculated using standard formulae[4]:

MIDARM MUSCLE CIRCUMFERENCE (MAMC) (cm) = MAC – (3.14 x TSF)

MIDARM MUSCLE AREA (MAMA) (cm^2) = $(MAMC)^2 / 4 \times 3.14$

MIDARM FAT AREA (MAFA) (cm^2)	= $[MAC^2/(4x3.14)]$ - MAMA
FAT / MUSCLE INDEX (F/M)	= MAFA / MAMA

SPIROMETRY

Spirometry was performed using standard equipment at the outpatient departments of Department of Thoracic Medicine, Government General Hospital and at Institute of Thoracic Medicine. FEV_1 / FVC ratio of <0.70 was used to define airflow obstruction. Mild, moderate and severe airflow obstructions were defined as FEV_1 >=80% predicted (stage 1 of GOLD classification), 50 – 80% predicted (stage 2a) and <50% of predicted (stage 2b and 3) respectively[1].

LABORATORY INVESTIGATIONS

Serum prealbumin was done at a private lab using standard immunoturbidimetric method[100].

The method gives a reference value of 20 – 40mg%.

Serum albumin was measured using spectrophotometric method[101].

The reference value was 3.5-5 g/dl.

RESULTS

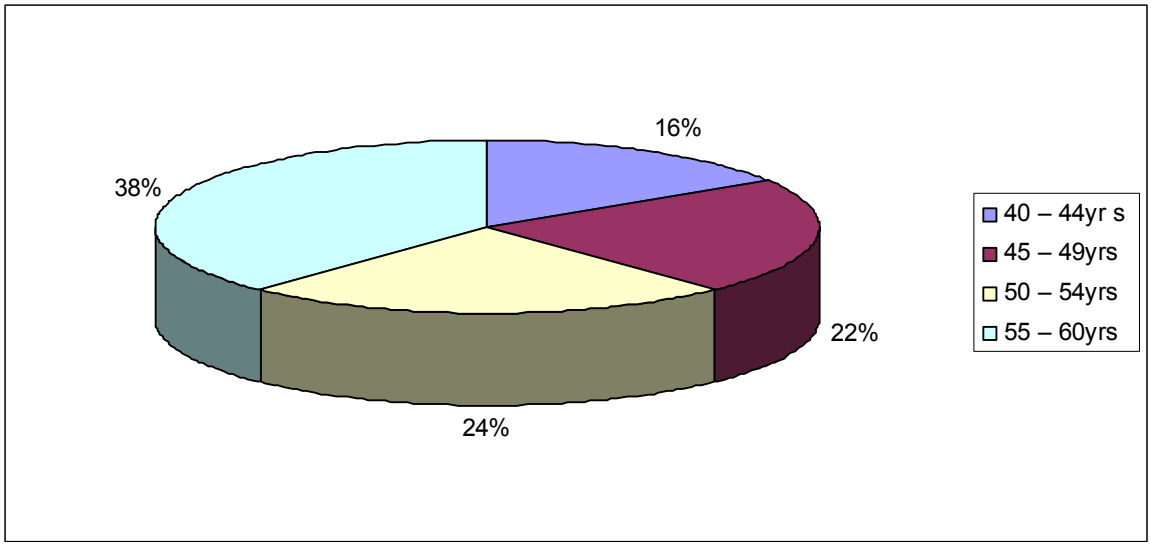
The study population included 50 patients, who were examined and evaluated. The following are the findings.

Table 1:Study Population Characteristics

Parameter	Mean	S.D
Age	51.32 yrs	5.85
Weight	55.1 kg	11.1
Height	1.60 m	0.07
Midarm circumference (MAC)	22.9 cm	3.6
Triceps skinfold (TSF)	1.31 cm	0.43
Body Mass Index (BMI)	21.40	3.56
Midarm Muscle Circumference (MAMC)	18.9 cm	2.38
Midarm Muscle Area (MAMA)	28.9 cm^2	7.40
Midarm Fat Area (MAFA)	14.2 cm^2	7.36
Fat/Muscle Ration (F/M)	0.47	0.11
Prealbumin	29.41mg%	7.98
Albumin	3.8g%	0.39
FEV_1	65.6%	15.52

Table 2: Age Distribution

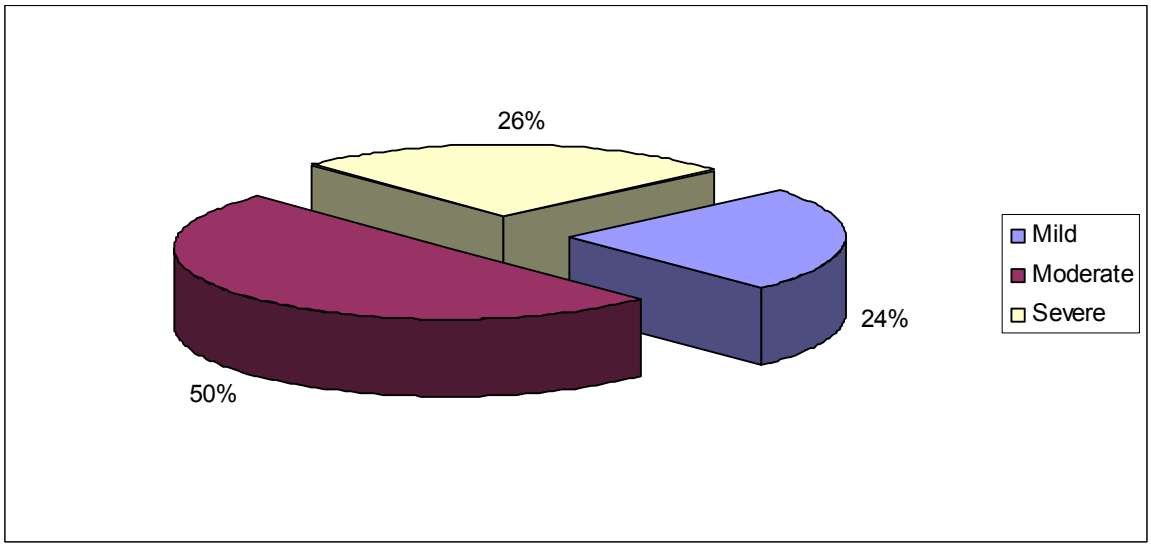
Age group	Number	Percentage
40 – 44	8	16%
45 – 49	11	22%
50 – 54	12	24%
55 – 60	19	38%



The average age of the study population was 51.32 years. Most of the patients (62%) were in the age group between 50 and 60 years.

Table 3: COPD SEVERITY (Based on FEV_1)

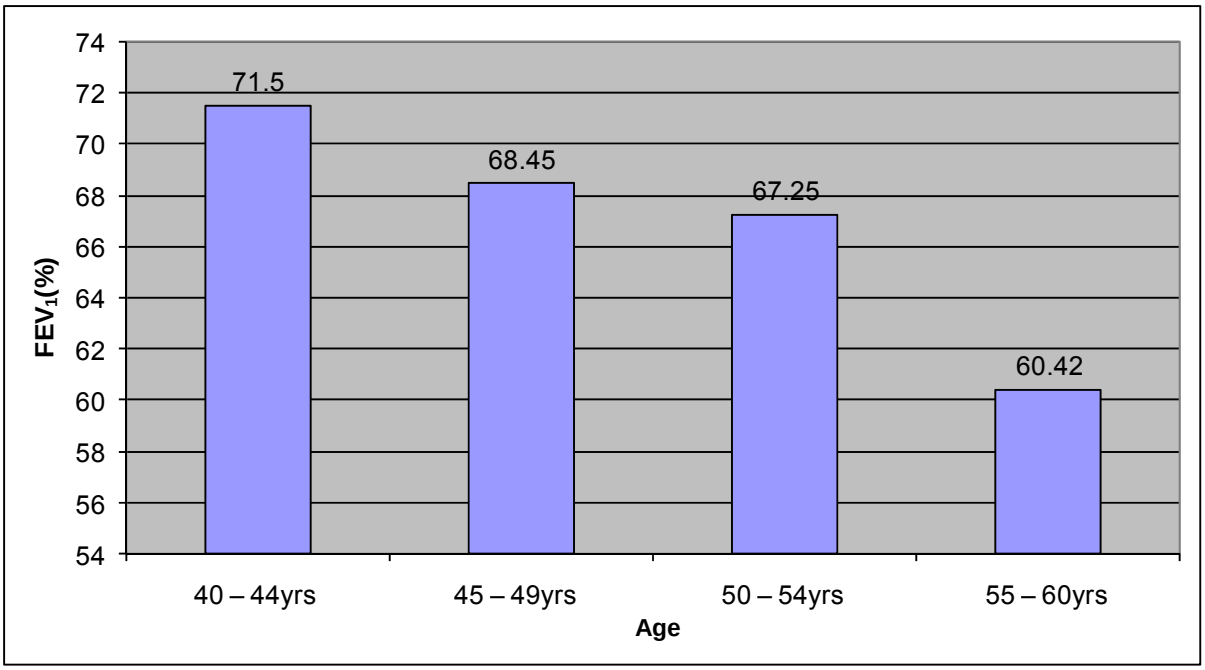
Degree of Obstruction	FEV_1 (% predicted)	Number	Percentage
Mild	>=80	12	24%
Moderate	50 – 79	25	50%
Severe	<50	13	26%



Of the 50 patients in the study, 12 (24%) had mild airway obstruction, 25 (50%) had moderate airway obstruction, and 13 (26%) had severe airway obstruction

Table 4: Relation between age and severity of obstruction

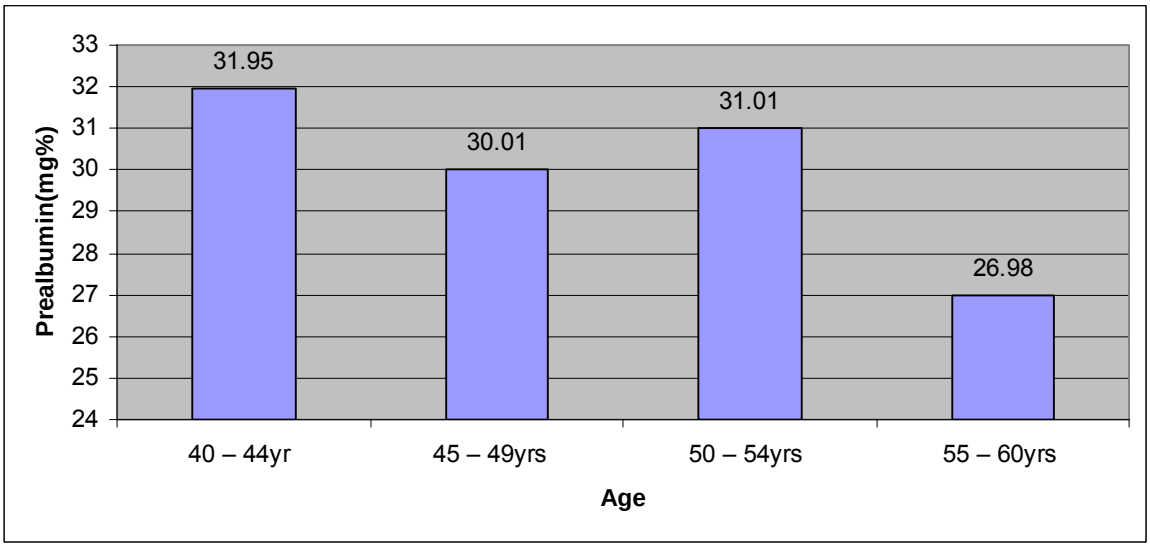
Age	Avg. FEV_1	Standard Deviation	One way ANOVA
40 – 44	71.50	12.64	P = 0.2922 Not Significant
45 – 49	68.45	15.67	
50 – 54	67.25	13.45	
55 – 60	60.42	17.22	



The difference in the degree of airway obstruction among the different age groups was not statistically significant.

Table 5: Relation between age and serum prealbumin

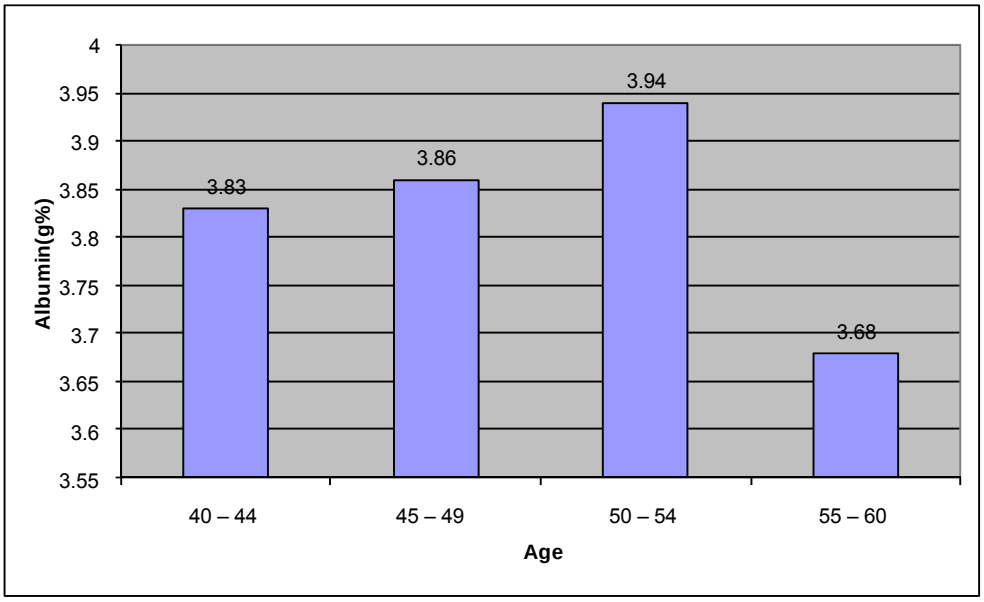
Age	Avg. prealbumin	Standard Deviation	One way ANOVA
40 – 44	31.95	7.52	P = 0.3848 Not Significant
45 – 49	30.01	6.22	
50 – 54	31.01	8.02	
55 – 60	26.98	8.93	



There was no significant difference in prealbumin value among different age groups.

Table 6: Relation between age and serum albumin

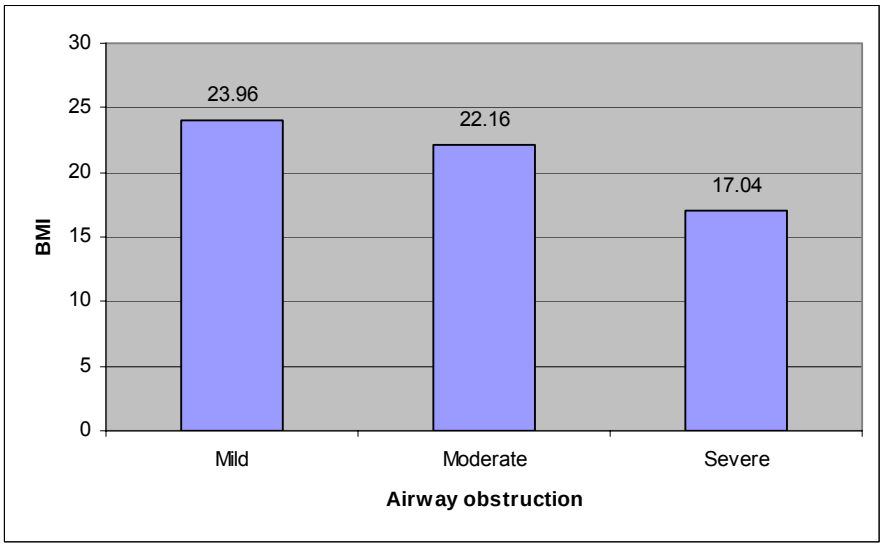
Age	Avg. Albumin	Standard Deviation	One way ANOVA
40 – 44	3.83	0.38	P = 0.3159 Not Significant
45 – 49	3.86	0.37	
50 – 54	3.94	0.38	
55 – 60	3.68	0.40	



There was no significant difference in serum albumin among different age groups.

Table 7: Relation between Airway Obstruction and BMI

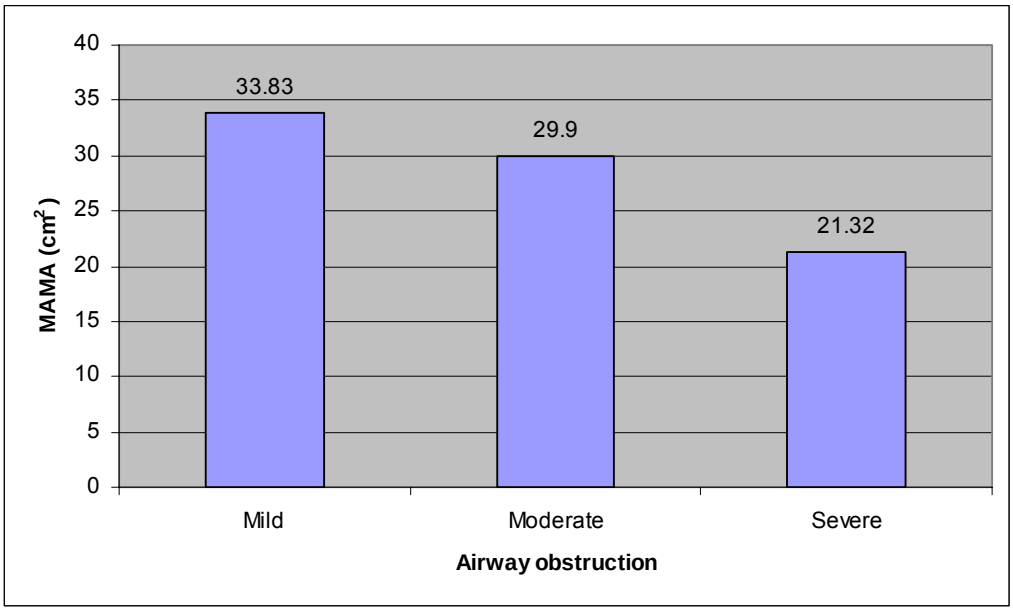
Airway Obstruction	Mean BMI	Standard Deviation	One way ANOVA
Mild (n=13)	23.96	1.20	P = < .001 Not Significant
Moderate (n=25)	22.16	3.28	
Severe (n=12)	17.04	1.27	



There was a significant difference in BMI value in patients with severe airway obstruction as compared to those with mild and moderate obstruction. However, the difference between the first two groups (mild and moderate obstruction) was not statistically significant.

Table 8: Relation between Airway Obstruction and Midarm Muscle Area (MAMA)

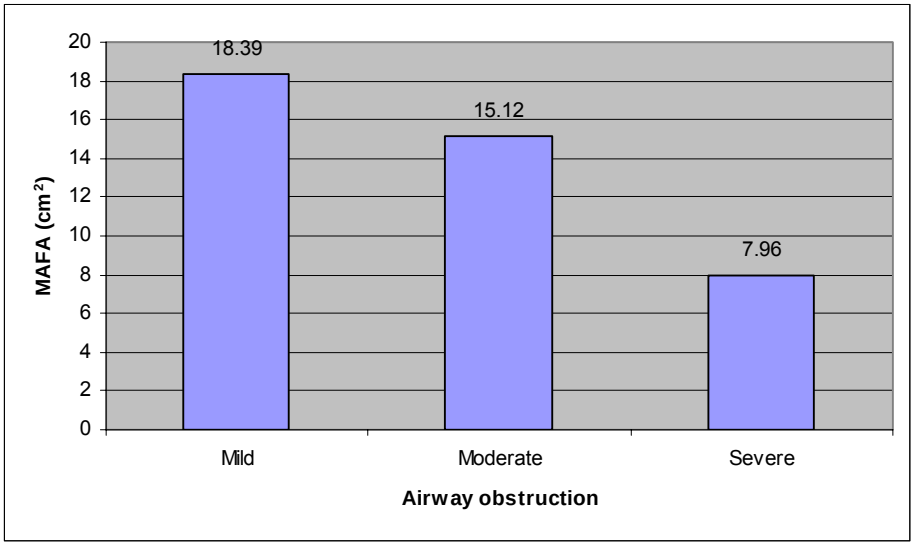
Airway Obstruction	Mean MAMA	Standard Deviation	One way ANOVA
Mild (n=13)	33.83	4.03	P = < 0.001 Significant
Moderate (n=25)	29.90	7.50	
Severe (n=12)	21.32	3.23	



There was a significant difference in MAMA value in patients with severe airway obstruction as compared to those with mild and moderate obstruction. However, the difference between the first two groups (mild and moderate obstruction) was not statistically significant.

Table 9: Relation between Airway Obstruction and Midarm Fat Area (MAFA)

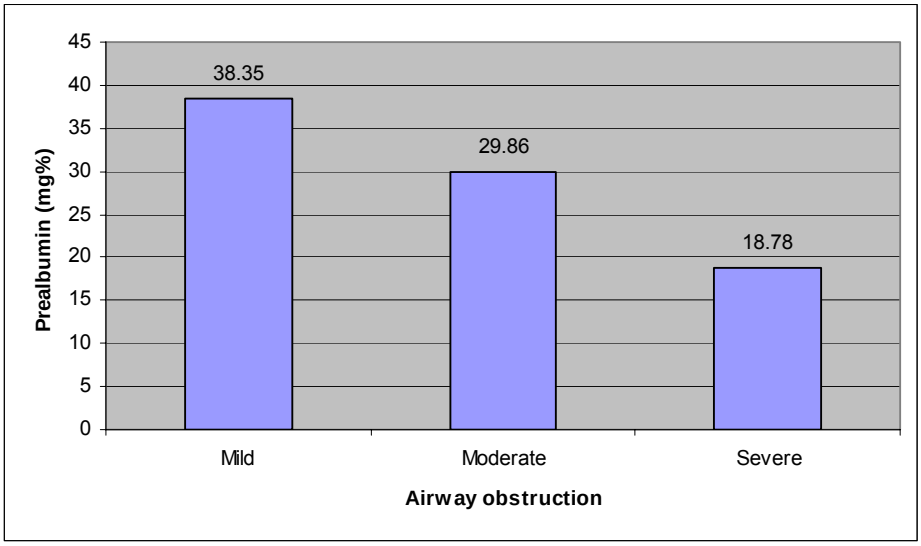
Airway Obstruction	Mean MAFA	Standard Deviation	One way ANOVA
Mild (n=13)	18.39	3.67	
Moderate (n=25)	15.12	8.56	
Severe (n=12)	7.96	1.37	P = 0.006 Significant



There was a significant difference in MAFA value in patients with severe airway obstruction as compared to those with mild and moderate obstruction. However, the difference between the first two groups (mild and moderate obstruction) was not statistically significant.

Table 10: Relation between Airway Obstruction and Serum Prealbumin

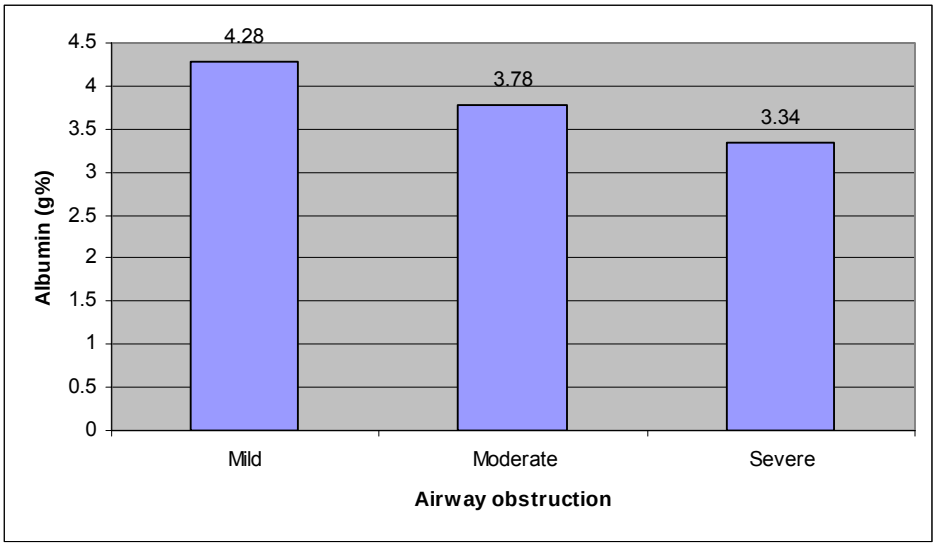
Airway Obstruction	Mean Serum Prealbumin	Standard Deviation	One way ANOVA
Mild (n=13)	38.35	3.19	
Moderate (n=25)	29.86	4.71	
Severe (n=12)	18.78	2.45	P < 0.0001



There was a statistically significant difference between the Serum Prealbumin level and degree of airway obstruction among all three groups.

Table 11: Relation between Airway Obstruction and Serum Albumin

Airway Obstruction	Mean Serum Albumin	Standard Deviation	One way ANOVA
Mild (n=13)	4.28	0.15	P = 0.01
Moderate (n=25)	3.78	0.23	
Severe (n=12)	3.34	0.17	



There was a statistically significant difference between the Serum Albumin level and degree of airway obstruction among all three groups

Table 12: Correlation of Severity of Airway Obstruction

with other parameters

Parameter	BMI	MAMA	MAFA	F/M	Pre Alb.	Alb.
r Value	0.75	0.69	0.55	0.58	0.76	0.68
P value	0.001	0.001	0.001	0.001	0.001	0.001

0-0.2	poor correlation	0.2-0.4	fair
0.4-0.6	moderate	0.6-0.8	substantial
0.8-1.0	good		

Table 13: Quartile distribution of Body Mass Index according to severity of airway obstruction

BMI	Severity of airway obstruction			Significance
	Mild	Moderate	Severe	
<P25 (n=13)	0 (0%)	3 (6%)	10 (20%)	p < 0.01
P 26-75 (n=24)	4 (8%)	18 (36%)	2 (4%)	
> P 75 (n=13)	9 (18%)	4 (8%)	0 (0%)	

P- Percentile

Of the 12 (24%) patients with severe airway obstruction, 10 patients were found to be in the lower quartile of body mass index of the study population.

Table 14: Severity of airway obstruction in the under nourished

BMI <18.5 kg/m^2 (n=14)	Severity of airway obstruction			Significance
	Mild	Moderate	Severe	
	0	3	11	$p < 0.01$

Out of the 50 patients, 14 (28%) were found to have a BMI<18.5 (under nourished status). Of these, 3 had moderate airway obstruction and 11 had severe airway obstruction.

Table 15: Quartile distribution of Midarm Muscle Area according to severity of airway obstruction

MAMA	Severity of airway obstruction			Significance
	Mild	Moderate	Severe	
<P25 (<23.7) (n=13)	0 (0%)	4 (8%)	9 (18%)	p < 0.01
P 26-75 (23.7-32.9) (n=24)	6 (12%)	15 (30%)	3 (6%)	
> P 75 (>32.9) (n=13)	7 (14%)	6 (12%)	0 (0%)	

P – percentile

Of the 12 (24%) patients with severe airway obstruction, 9 patients were found to be in the lower quartile of Midarm Muscle Area of the study population.

Table 16: Quartile distribution of Midarm Fat Area according to severity of airway obstruction

MAFA	Severity of airway obstruction			Significance
	Mild	Moderate	Severe	
<P25 (<9.8)	0 (0%)	2 (4%)	11 (22%)	p < 0.5
P 26-75 (9.8-17.1)	5 (10%)	18 (36%)	1 (2%)	
> P 75 (>17.1)	8 (16%)	5 (10%)	0 (0%)	

P – Percentile

Of the 12 (24%) patients with severe airway obstruction, 11 patients were found to be in the lower quartile of Midarm Fat Area in the study population.

Table 17: Severity of airway obstruction in patients with Hypoalbuminemia

Sr. Albumin<3.5g%	Severity of airway obstruction			Significance
	Mild	Moderate	Severe	
	0	1	8	$p < 0.01$

9 (18%) patients in the study were found to have a Serum albumin level of less than 3.5g%. Of these, 1 patient had moderate airway obstruction and 8 had severe airway obstruction.

DISCUSSION

Several relevant observations were made in the present study. Comparisons of the present study with previous studies is difficult because the criteria for malnutrition are not universally accepted.

1. AGE:

The average age of the study population in the present study was 51.32 years (Table 1). In a similar study done by Soler et al[4], the average age was 69 years. The patients in the present study were in the age group of 40 to 60 years (Table 2). This was chosen because the FEV_1 has been found to progressively decrease as the age advances. The selection of the patients within a narrower age group was done to ensure uniformity in the study group.

In the study, there was no statistically significant difference in the various nutritional parameters and biochemical parameters among the different age groups.

2. SEX:

All the patients selected for the study were male. This was done because the biochemical parameter prealbumin has been found to vary between males and females. Females have been found to have a lower value of prealbumin. The study by Soler et al[4] included 177 male patients and 1 female patient.

3. FORCED EXPIRATORY VOLUME IN THE FIRST SECOND:

The average FEV_1 of the population in the present study was 65.6 (percent predicted) compared with 44.6 (percent predicted) in the study by Soler et al[4]. The population was divided into mild, moderate and severe airway obstruction based on GOLD criteria[1].

In the present study, 12 (24%) patients were found to have severe obstruction with $FEV_1$30-50%, 25 (50%) patients had moderate airway obstruction with FEV_1 between 50-80%, and 13 (26%) had mild airway obstruction with FEV_1. Patients with FEV_1 of <30% were not selected as these patients had frequent exacerbations of symptoms (Table 3).

FEV_1 did not vary significantly among the different age groups.

4. ANTHROPOMETRIC MEASURES:

The following anthropometric measures were analysed in the study population:

a) WEIGHT AND HEIGHT:

The average weight of the population in the present study was 55.1 kg (Table 1) compared with 74.1 kg in the study by Soler et al[4]. The average height of the population in the present study was 1.60m (Table 1) compared with 1.62m in the study by Soler et al.[4] The difference can probably be explained by the fact that the present study was done on an Indian population which has a lower average body weight than Western population.

b) BODY MASS INDEX:

The average BMI of the population in the present study was 21.4 kg/m^2 (Table 1) compared with 28.2 kg/m^2 in the study by Soler et al[4]. There are no standards available for the BMI in the Indian population.

In the present study, a correlation was found between a lower BMI and the severity of airway obstruction. BMI of less than 18.5, which is considered as under-nutrition in general population[102] was found in 14

(28%) patients. Of these 3 were having moderate airway obstruction and 11 were having severe airway obstruction (Table 14). There was no statistically significant difference in the BMI between groups with mild and moderate airway obstruction. There was a significant difference in the mean BMI between the population with severe airway obstruction and the above two groups (Table 7). The present study found a substantial correlation between low BMI and severity of airway obstruction of 0.75 (Table 12).

In the study by Soler et al[4], BMI less than 20 kg/m^2 was taken as undernourished. 3 of those patients were found to have moderate airway obstruction and 4 were found to have severe airway obstruction.

c) MID ARM CIRCUMFERENCE:

The average midarm circumference in the present study was 22.9 cm (Table 1). Anthropometric studies have shown that a midarm circumference of less than 23 cm signifies under-nutrition[99].

d) TRICEPS SKINFOLD THICKNESS:

The average triceps skinfold thickness in the present study population was 1.31 cm (Table 1). Although there are no standards, population studies have found a value of 0.9 – 2.1 cm[98].

e) MIDARM MUSCLE AREA (MAMA):

This value was used to assess the muscle mass of the patient. The mean MAMA in the present study was found to be 28.9 cm^2 (Table 1).Of these 13 (26%) of the patients were found to be in the lower quartile (< 25^{th} percentile) of the distribution. Of these, 9 patients had severe airway obstruction and 4 patients had moderate airway obstruction. This set of patients were considered as having severe muscle mass depletion (Table 15).

In the study by Soler et al[4], out of 177 patients, 84 (47%) of the patients were found to have muscle mass depletion. Of these, 43 patients had severe airway obstruction.

The present study showed a statistically significant difference in MAMA between the population group with severe airway obstruction and those with mild and moderate airway obstruction (Table 8).

The present study also showed a correlation between decrease in muscle mass and severity of airway obstruction (with a correlation coefficient of 0.69) (Table 12).

f) MIDARM FAT AREA (MAFA):

This measure was used to assess the fat store of the body. The mean MAFA in the present study was found to be 14.2 cm^2 (Table 1). Of these 13 (26%) of the patients were found to be in the lower quartile (< 25^{th} percentile) of the distribution. Of these, 11 patients had severe airway obstruction and 2 patients had moderate airway obstruction. This set of patients were considered as having severe fat store depletion (Table 16).

In the study by Soler et al[4], out of 177 patients, 34 (19%) of the patients were found to have muscle mass depletion. Of these, 20 patients had severe airway obstruction.

The present study showed a statistically significant difference in MAFA between the population group with severe airway obstruction and those with mild and moderate airway obstruction. There was no significant difference between the latter two groups (Table 9).

The present study also showed a correlation between decrease in muscle mass and severity of airway obstruction (with a correlation coefficient of 0.55) (Table 12).

The degree of muscle mass depletion was found to correlate more strongly with the degree of airway obstruction than the degree of fat depletion. This corresponded with the findings in the study by Soler et al[4].

5. MEASURES OF VISCERAL PROTEIN STORES:

Serum prealbumin and serum albumin were used as the measures of visceral protein in the present study.

a. SERUM PREALBUMIN:

The average prealbumin value in the study population was 29.41 mg/dl (Table 1). The present study showed an inverse correlation between the level of prealbumin and the severity of airway obstruction (with a correlation coefficient of 0.76) (Table 12). There was a statistically significant difference in the average values between the three groups of airway obstruction (mild, moderate and severe) (Table 10).

In the study by Braun et al[96], the prealbumin level was correlated with Arterial oxygen saturation. A statistically significant correlation value of 0.42 was found in the study.

Studies done previously have demonstrated that prealbumin is not an accurate marker for malnutrition in various disease states, as it is influenced by other factors.

The present study however, demonstrated that there is a significant correlation between severity of airway obstruction and decrease in serum prealbumin.

b) SERUM ALBUMIN:

The average serum albumin in the study population was 3.8 g/dl (Table 1). The present study showed a statistically significant inverse correlation between the degree of airway obstruction and level of serum albumin (with a correlation coefficient of 0.68) (Table 12). There was a statistically significant difference in the average albumin values between the three groups (mild, moderate and severe airway obstruction) (Table 11).

9 (18%) of the 50 patients were found to have a serum albumin value of less than 3.5g/dl. Of these, 8 patients had severe airway obstruction and 1 patient had moderate airway obstruction (Table 17).

In the study done by Soler et al[4], of the 177 patients, 17 (9.6%) patients were found to have a serum albumin value of less than 3.5g/dl. This value was not statistically significant.

STUDY LIMITATIONS

1. The study is a hospital based study and may not be representative of the general population.
2. As the study is designed as a cross sectional study, the present analysis will be unable to elucidate the prognostic indications of the nutritional indices.
3. The patients were on different durations of treatment and different drugs. These may have an effect on the findings of the study.
4. Spirometry is a user dependent method of assessment and may not always accurately assess the degree of airway obstruction.
5. The study population involved a set of patients within a narrow age group. The findings may not be extrapolated to other age groups
6. The study population did not include females.

CONCLUSIONS

1. A significant number of outpatients with Chronic Obstructive Pulmonary Disease were found to be undernourished.
2. The anthropometric measures of nutrition (Body Mass Index, Body muscle mass, Body fat stores) were related inversely with the degree of airway obstruction.
3. Measures of visceral protein stores (Serum prealbumin and Serum albumin) correlated inversely with severity of airway obstruction.

BIBLIOGRAPHY

1. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2006. *Available from: www.goldcopd.com.*

2. Landbo C, Prescott E, Lange P, Vetbo J, Almdal TP. Prognostic value of nutritional status in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 160: 1856-61.

3. Gray-Donald K, Gibbons L, Shapiro SH, Maclean PT, Martin JG. Nutritional status and mortality in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996; 153: 961-6.

4. Soler JJ, Sanchez L, Roman P, Martinez MA, Perpina M. Prevalence of malnutrition in outpatients with stable chronic obstructive pulmonary disease. *Arch Bronconeumol* 2004; 40: 250-8.

5. Schols AMWJ, Soeters PB, Mostert, et al. Energy balance in chronic obstructive pulmonary disease. *Am rev repir dis* 1991; 143:1248-52.

6. World Health Report, Geneva: World Health Organization. *Available from http://www.who.int/whr/2000/en/statistics. 2000.*

7. Lopez AD, Shibya K, Mathers CD, Hansell AL, Held LS, et al. Chronic obstructive pulmonary disease: current burden and future projections. *Eur Respir J* 2006; 27(2): 397-412.

8. Pellegrino R, Viegi G, Brusow V, Crap RO, Brugo F, Caraburi R et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005; 26(5): 948-68.

9. Pauwels RA, Rabe KF. Burden and clinical features of chronic obstructive pulmonary disease. *Lancet* 2004; 364: 613-20.

10. Xu F, Yin X, Zhang M, Shen H, Lu L, Xu Y. Prevalence of physician diagnosed COPD and its association with smoking among urban and rural residents in regional mainland China. *Chest* 2005; 128: 2818-23.

11. Kim DS, Kim YS, Jung KS, Chang JH, et al. Prevalence of chronic obstructive pulmonary disease in Korea: a population based spirometry survey. *Am J Respir Crit Care Med* 2005; 172: 842-7.

12. Menezes AM, Perez-Padilla R, Jardim JR, Muino A, Lopez MV, Valdivia G, Montes de Oca M, et al. Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. *Lancet* 2005; 365: 1875-81.

13. Stoller JK, Aboussouan LS. Alpha 1-antitrypsin deficiency. *Lancet* 2005; 365(9478): 2225-36.

14. US Surgeon General. The health consequences of smoking: chronic obstructive pulmonary disease. Washington D.C.: *US Department of Health and Human Services*; 1984.

15. Burrows B, Knudson RJ, Cline MG, Lebowitz MD. Quantitative relationships between cigarette smoking and ventilatory function. *Am Rev Respir Dis* 1977; 115: 195-205.

16. Becklake MR. Occupational exposures: evidence for a causal association with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1989; 14: 85-91.

17. Trupin L, Ernest G, San Pedro M, Balmes JR, Eisner MD, Yelin E, et al. The occupational burden of chronic obstructive pulmonary disease. *Eur Respir J* 2003; 22(3): 462-9.

18. Matheson MC, Benke G, Raven J, Sim MR, Kromhout H, Vermuelen R, et al. Biological dust exposure in the workplace is a risk factor for chronic obstructive pulmonary disease. *Thorax* 2005; 60(8): 645-51.

19. Hnizdo E, Sulivan PA, Bang KM, Wagner G. Association between chronic obstructive pulmonary disease and employment by industry and occupation in the US population: a study of data from the Third National Health and Nutrition Examination Survey. *Am J Epidemiol* 2002; 156(8): 738-46.

20. Ezzati M. Indoor air pollution and health in developing countries. *Lancet* 2005; 366: 104-6.

21. Smith KR, Mehta S, Maeusezahl-Feuz M. Indoor air pollution from household solid fuel use. Geneva: World Health Organization; 2004.

22. Tager IB, Segal MR, Speizer FE, Weiss ST. The natural history of forced expiratory volumes. *Am rev Respir Dis* 1988; 138(4): 837-49.

23. National Heart, Lung and Blood Institute. Morbidity and mortality chartbook on cardiovascular, lung and blood diseases. Bethesda, Maryland: US Department of Health and Human Services, Public Health Service, National Institutes of Health, 2004. *Accessed at: http://www.nhlbi.nih.gov/resources/docs/cht-book.htm.*

24. Mannino DM, Homa D, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance – United States, 1971-2000. *MMWR Surveill Summ* 2002; 51: 1-16.

25. Prescott E, Lange P, Vestbo J. Socioeconomic status, lung function and admission to hospital for COPD: results from the Copenhagen City Heart Study. Eur Respir J 1999; 13(5): 1109-14.

26. Saetta M, Turato G, Maestrelli P, Mapp CE, Fabbri LM. Cellular and structural bases of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 163(6): 1304-9.

27. Hogg JC, Chu F, Utokaparch S, Woods R, Elliott WM, Bazatu L, et al. The nature of small airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med* 2004; 350(26): 2645-53.

28. Cosio MG, Majo J. Inflammation of the airways and lung parenchyma an COPD: role of T cells. *Chest* 2002; 121: 160-5.

29. Wright JL, Levy RD, Churg A. Pulmonary hypertension in chronic obstructive pulmonary disease: current theories of pathogenesis and their implications in treatment. *Thorax* 2005; 60(7): 605-9.

30. Barnes PJ, Shapiro SD, Pauwels RA. Chronic obstructive pulmonary disease: molecular and cellular mechanisms. *Eur Respir J* 2003; 22(4):672-88.

31. Barnes PJ. Mediators of chronic obstructive pulmonary disease. *Pharmocol Rev* 2004; 56(4): 515-48.

32. Rahman I. Oxidative stress in pathogenesis of chronic obstructive pulmonary disease: cellular and molecular mechanisms. *Cell Biochem Biophys* 2005; 43(1): 167-88.

33. Barbera JA, Peinado VI, Santos S. Pulmonary hypertension in chronic obstructive pulmonary disease. *Eur Respir J* 2003; 21(5):892-905.

34. Pauwels R. Global initiative for chronic obstructive pulmonary disease (GOLD): time to act. *Eur Respir J* 2001; 18: 901-2.

35. Fletcher C, Peto R. The natural history of chronic airflow obstruction. *Br Med J* 1977; 1: 1645-8.

36. Anthonisen NR, Wright EC, Hodgkin JE. Prognosis in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1986; 133: 14-20.

37. Hospers JJ, Postino DS, Rijcken B et al. Histamine airway hyper-responsiveness and mortality from chronic obstructive pulmonary disease: a cohort study. *Lancet* 2000;356:1313-17.

38. American Thoracic Society. Dyspnea: mechanisms, assessment and management: a consensus statement. *Am J Respir Crit Care Med* 1999; 159: 321-40.

39. Celli BR, Mac Nee W. Standards for the diagnosis and treatment of chronic obstructive pulmonary disease. *Eur Respir J* 2004; 23: 932-46.

40. Mahler DA, Weinburg DH, Wells CK et al. The measurement of dyspnea: contents, inter observer agreement and physiologic correlates of two new clinical indices. *Chest* 1984; 85: 751-8.

41. Nishimura K, Izumi T, Tsukino M et al. Dyspnea is a better predictor of 5- year survival than airway obstruction in patients with COPD. *Chest* 2002; 121: 1434-40.

42. Neff TA, Petty TL. Long term continuous oxygen therapy in chronic airway obstruction. *Ann Intern Med* 1995; 72: 621-5.

43. Postma DS, Burema J, Gimeno F et al. Prognosis in severe chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1979; 119: 357-67.

44. Burrows B, Earle RH. Prediction of survival in patients with chronic airway obstruction. *Am Rev Respir Dis* 1969; 99: 865-71.

45. Casanova C, Cote C, de Torres JP, et al. Inspiratory - to - total lung capacity ratio predicts mortality an patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 171: 591-7.

46. Stevens D, Sharma K, Szidan P, et al. Severe pulmonary hypertension associated with COPD. *Ann Transplant* 2000; 5: 8-12.

47. Chiriat A, Bugnet AS, Kadaoui N, et al. Severe pulmonary hypertension and chronic obstructive pulmonary disease . *Am J Respir Crit Care Med* 2005; 172: 189-94.

48. Englen MP, Schols AM, Baken WC, et al. Nutritional depletion an relation to respiratory and peripheral skeletal muscle function an out patients with COPD. *Eur Respir J* 1994; 7: 1793-7.

49. Schols AM, Socters PB, Baken WC, et al. Prevalence and characteristics of nutritional depletion an patients with stable COPD eligible for pulmonary rehabilitation. *Am Rv Respir Dis* 1993; 147: 1151-6.

50. Wilson DO, Rogers RM, Wright EC, et al. Body weight in chronic obstructive pulmonary disease: the National Institutes of Health intermittent positive pressure breathing trial. *Am Rev Respir Dis* 1989; 139: 1435-8.

51. Schols AM, Slangen J, Volovics L, et al. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 157: 1791-7.

52. Marquis K, Debugare R, Lacasse Y, et al. Midthigh cross sectional area is better predictor of mortality than body mass index an patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002; 166: 809-13.

53. Soler JJ, Sanchez-Sanchez L, Martinez Garcia MA, et al. Midarm muscle area is a better predictor of mortality than body

mass index in chronic obstructive pulmonary disease. *Chest* 2005; 128(4): 2108-15.

54. Weisman I. Cardiopulmonary exercise testing in the preoperative assessment for lung function surgery. *Sem Thorac Cardiac Surg* 2001; 13: 116-25.

55. Pinto-Plata VM, Cote C, Cabral H, et al. The 6 minute walk distance: change over time and value as a predictor in severe COPD. *Eur Respir J* 2004; 23: 28-33.

56. Chambellan A, Chailleux E, Similoski T. The ANTADIR observatory group. Prognostic value of hematocrit in patients with severe obstructive pulmonary disease receiving long term oxygen therapy. *Chest* 2005; 128: 1201-8.

57. Celli BR, Cote CG, Martin JM, et al. The body mass index, airflow obstruction, dyspnea and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004; 350: 1005-12.

58. Wilson DO, Rogers RM, Sander MH, et al. Nutritional intervention in malnourished patients with emphysema. *Am Rev Respir Dis* 1986; 134: 672-7.

59. Ferguson GT, Cherniak RM. Management of chronic obstructive pulmonary disease. *N Engl J Med* 1993; 327: 1017-22.

60. Rochester DF, Braun NMT. Determinants of maximal inspiratory pressure in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1985; 132: 42-7.

61. Mota-Casals S. Inspiratory muscle performance in chronic obstructive pulmonary disease. *Arch Bronchoneumol* 2005; 41: 601-6.

62. Verea Hernandez H. Corticosteroids in exacerbation of chronic obstructive pulmonary disease. *Arch Bronchoneumol* 2005;41: 641-2.

63. Dureuil G, Matuscak Y. Alteration in nutritional status and diaphragm muscle function. *Reprod Nut Dev* 1998: 175-80.

64. Gea J, Orcozo-Levi M, Barreiro E. Muscle pathology in patients with chronic obstructive pulmonary disease. *Nutr Hosp* 2006: 62-8.

65. Foley RJ, Zu Wallack R. The impact of nutritional depletion in chronic obstructive pulmonary disease. *J Cardiopulm Rehabil* 2001: 1041-52.

66. Sridhar MK. Nutrtion and lung health. *Proc Nutr Soc* 1999; 58: 303-8.

67. Sahebjami H, Domino M. Effects of repeated cycles of starvation and refeeding on lungs of growing rats. *J Appl Physiol* 1992; 73: 2349-54.

68. Celli B, Goldstein R, Jardim J, Knobil K. Future perspectives in chronic obstructive pulmonary disease. *Respir Med* 2005; 99: 41-8.

69. Acosti J, Gomez-Tellou, Ruiz S. Assessment of nutrition in acutely ill patients. *Nutr Hosp* 2005; 20: 5-8.

70. Slinde F, Gronberg A, Engstrom CP, Rossander-Hulther L, Larsson S. Body composition by bioelectrical impedance predicts mortality in chronic obstructive pulmonary disease patients. *Respir* Med 2005; 99: 1004-9.

71. Gruijjaro C, Massy ZA, Wiederkehr MR, et al. Serum albumin and mortality after renal transplantation. *Am J Kidney Dis* 1996; 27: 117-8.

72. Klonoff-Cohen H, Barnett-Connor EL, Edelstein SL. Albumin levels as a predictor of mortality in the healthy elderly. *J Clin Epidemiol* 1992; 45: 207.

73. Goldwasser P, Feldman J. Asoociation of serum albumin and mortality risk. *J Clin Epidemiol* 1997; 50: 693.

74. Courtney ME, Greene HL, Folk CC, et al. Rapidly declining serum albumin values in newly hospitalized patiens: prevalence, severity and contributory factors. *JPEN* 1982; 6: 143.

75. Rothschild MA, Oratz M, Schreiber SS. Serum albumin. *Hepatology* 1988; 8: 385.

76. Schols AM, Mostert R, Soeters PB, Greve LH, Wouters EF. Nutrtional state and exercise performance in patients with chronic obstructive pulmonary disease. *Thorax* 1989;44:937-41.

77. Katsura H, Ogata M, Kida K. Factors determining outcome in elderly patients with severe COPD on long-term domiciliary oxygen therapy. *Monaldi Arch Chest Dis* 2001; 56: 195-201.

78. Bernstein L. Measurement of visceral protein status in assessing protein and energy malnutrition: standard of care (Prealbumin an Nutrtional Care Consensus Group). *Nutrition*; 11: 169-75.

79. Roza AM, Tuitt D, Shizgal HM, et al. Transferrin- a poor marker of nutritional status. *JPEN* 1984; 8: 523.

80. Forse RA, Shizgal HM. Serum albumin and nutritional status. *JPEN* 1980; 4: 450-55.

81. Shetty PS, Jung RT, Watrasiewicz KE, eta al. Rapid turnover transport protein: an index of protein calorie malnutrition. *Lancet* 1979; 2: 230-32.

82. Ingenbleek Y, Van Den Schrek HG, De Nayer P. Measurement of prealbumin as an index of protein calorie malnutrition. *Lancet* 1976; 2: 106-12.

83. Ferguson RP, o' Connor P, Crabtree B, et al. Serum albumin and prealbumin as predictors of clinical outcome of hospitalized

elderly nursing home residents. *J Am Geriatr Soc* 1993; 41: 545-48.

84. Boury J, Milano G, Caldani C, et al. Assessment of nutritional proteins during the parenteral nutrition of cancer patients. *Ann Clin Lab Sci*; 1982: 158-61.

85. Winkler MF, Pomp A, et al. Transitional feeding: the relationship between nutritional intake and plasma protein concentrations. *J Am Dietitic Assoc* 1989; 89: 969-75.

86. Cynober L, Prugnaud O, Liovet N, et al. Serum transthyretin levels in patients with burn injury. *Surgery* 1991; 109: 640-44.

87. Korda Y, Goodman DS, et al. The amino acid sequence of human plasma prealbumin. *J Biol Chem* 1974; 249: 6796-802.

88. Robbins J, Cheng SY, Grenshengorn MC, et al. Thyroid transport proteins of plasma: molecular properties and biosynthesis. *Rec Prog Horm Res* 1978; 34: 477-9.

89. Munro HN, Mc Gurdy RB, Hortz SC, et al. Protein nutrition in a group of free living elderly. *Am J Clin Nutr* 1987; 46: 586-90.

90. Sachs E, Burnstein LH. Protein markers of nutrition status as related to sex and age. *Clin Chem* 1986; 32: 339-45.

91. Goldberg DM, Brown D. Advances in the application of biochemical tests to diseases of the liver and biliary tract: their

role in diagnosis, prognosis and the elucidation of pathogenetic mechanisms. *Clin Biochem* 1987; 20: 127-31.

92. Carpenter YA et al. Plasma protein concentrations in nutritional assessment. *Proc Nutr Soc* 1982; 4: 405-16.

93. Bole JM, Garre MA, Youinou BY, et al. Nutritional status in intensive care unit patients: evaluation in 84 unselected patients. *Crit Care Med* 1983; 11: 87-89.

94. Delpeuch F, Cornu A, Chevalier P. The effect of iron deficiency anemia on two indices of nutritional status, prealbumin and transferring. *Br J Nutr* 1980; 43: 375-78.

95. Smith FR, Goodman DS. The effect of disease of the liver, thyroid and kidneys on the transport of vitamin A in human plasma. *J Clin Invest* 1971; 50: 2426-28.

96. Braun SR, Keim NL, Dixon RM, Anderdregg A, Shraggo ES. The prevalence and determinants of nutritional changes in chronic obstructive pulmonary disease. *Chest* 1984; 86: 558-63.

97. Olabinri BM, Olaleye MT, et al. Age- specific association between percent body fat and pulmonary function in apparently normal children in Ogbomoso, Ogo State, Nigeria. *African J Biomed Res* 2006; 9(2): 83-7.

98. Robert JM, Stanley PS, George MO. Height, weight and skinfold thickness of Michigan adults. *AJPH* 1980; 70(12): 1290-92.

99. Matthews AL et al. Mid upper arm circumference in adults. *Nutrition* 1995; 78: 887-92.

100. Dati F, et al Clinical guidelines to laboratory tests *Eur J Clin Chem Bio Chem* 1996; 34: 517-20.

101. Pesce J, Kaplan LA. Methods in clinical chemistry; Mosby Co. 1997.

102. Calle EE, Thun MJ, et al. Body mass index and mortality in a prospective cohort of US adults. *N Engl J Med* 1999; 341(13): 1097-105.

LIST OF ABBREVIATIONS

COPD	Chronic Obstructive Pulmonary Disease
GOLD	Global Initiative for Chronic Obstructive Pulmonary Disease
FEV_1	Forced Expiratory Volume in the first second
FVC	Forced Vital Capacity
BMI	Body Mass Index
MAC	Midarm Circumference
TSF	Triceps skinfold thickness
MAMC	Midarm Muscle Circumference
MAMA	Midarm Muscle Area
MAFA	Midarm Fat Area
F/M	Fat / Muscle index
TNF	Tumour Necrosis Factor
IL	Interleukin
TGF	Transforming Growth Factor
AHR	Airway Hyper responsiveness
PaO_2	Arterial partial pressure of oxygen
$PaCO_2$	Arterial partial pressure of carbon dioxide

LIST OF TABLES

PROFORMA FOR ASSESSMENT OF NUTRITIONAL STATUS IN COPD PATIENTS

Name:

Age:

Sex:

Address:

Occupation:

OP No.

Smoker Y/N:

Symptoms: h/o cough
h/o sputum production
h/o breathlessness

Co-morbidities: h/o Diabetes Mellitus
h/o Hypertension
h/o Coronary artery disease/ congestive heart failure
h/o liver disease
h/o Tuberculosis

Treatment History: Bronchodilators
Inhaled/systemic steroids
Anti tuberculous drugs

Family History: Diabetes Mellitus
Hypertension
Tuberculosis
Malignancy
Coronary Artery Disease

EXAMINATION:

Height (m):
Weight (kg):
Blood Pressure:
Pulse:
Midarm Circumference (cm):
Triceps Skinfold Thickness (cm):

Cardiovascular System:

Respiratory System:

Abdomen:

Central Nervous System:

INVESTIGATIONS:

Blood Glucose:
Blood Urea:
Serum Creatinine:
Serum Electrolytes:

Blood Counts: Hemoglobin: Total Count:
Differential Count: ESR:

Liver Function Tests:

MEASURES OF VISCERAL PROTEIN STORES:

Serum Albumin:

Serum Prealbumin:

ANTHROPOMETRIC MEASURES:

Body Mass Index:

Midarm Muscle Circumference:

Midarm Muscle Area:

Midarm Fat Area:

Fat/Muscle Ratio:

SPIROMETRY:

FEV_1 (Percent predicted):

FEV_1/FVC (Percentage):

Severity of airway obstruction: Mild / Moderate / Severe

PATIENT CONSENT FORM

STUDY TITLE:
"EVALUATION OF NUTRITIONAL STATUS IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE"

Study centre : Institute of Internal Medicine and Department of Thoracic Medicine

Madras Medical College

Patient's Name : _____

Patient's Age : _____

Identification No. : _____

Patient's may (√) these boxes

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

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

I understand that the sponsor of this clinical study, others working on the sponsor's behalf, the ethics committee and the regulatory authorities will not need my permission to look at my heath records both in respect to the 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. ☐

I agree to take part in the above study and to comply with instructions given during the study and to co-operate with the study team, and to immediately inform the study staff if I suffer from any deterioration of health or any unexpected or unusual symptoms. ☐

I hereby consent to participate in this study on "Evaluation of Nutritional status in patients with chronic obstructive pulmonary disease". I hereby give permission to undergo complete clinical examination, and diagnostic tests. ☐

Signature/Thumb impression _____ Place_____ Date_____
of the patient

Patient's Name and Address _____

_____

Signature of the Investigator _____ Place_____ Date_____

Study Investigator's Name _____