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**A Critical Evaluation of Prognostic Indicators of the Natural History of
Chronic Obstructive Pulmonary Disease (COPD).**

KHALID A. ANSARI

**FACULTY OF APPLIED SCIENCES
UNIVERSITY OF SUNDERLAND**

*A thesis submitted in partial fulfilment of the requirements of the University of Sunderland for
the Degree of Doctor of Philosophy*

The research was carried out in collaboration with Chest Clinic, Sunderland Royal Hospital,
Age Concern and Breathe Easy Group

March 2012

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Abbreviations

A	AECOPD AECB ATS ADL ADO AUC	Acute Exacerbation Of Chronic Obstructive Pulmonary Disease Acute Exacerbation Of Chronic Bronchitis American Thoracic Society Activity of Daily Living Age, Dyspnoea measured by MRC score and Airway Obstruction Area Under the Curve
B	B BMI BDI BLF BODS BOD BODE BODA BODAS BTS	Beta Body Mass Index Baseline Dyspnoea Index British Lung Foundation Body Mass Index, Airway Obstruction, Dyspnoea measured by MRC Body Mass Index, Airway Obstruction, Dyspnoea measured by MRC Body Mass Index, Airway Obstruction, Dyspnoea measured by MRC, Exercise capacity measured by six minute walk test. Body Mass Index, Airway Obstruction, Dyspnoea measured by MRC, Age Body Mass Index, Airway Obstruction, Dyspnoea measured by MRC, Age and smoking years. British Thoracic Society
C	CAO CDU CI COAD COLD CAL COPD CRDQ CRQ	Chronic Airflow Obstruction. Clinical Decision Units Confidence Interval Chronic Obstructive Airways Disease Chronic Obstructive Lung Disease Chronic Airflow Limitation Chronic Obstructive Pulmonary Disease Chronic Respiratory Disease Questionnaire Chronic Respiratory Questionnaire
D	DALY df DOS DOSE	Disability Adjusted Life Year Degree of freedom Dyspnoea, Airway Obstruction and Smoking history Dyspnoea, Airway Obstruction and Smoking status and Frequency of exacerbations.
E	ELF ERS Ex Est	European Lung Foundation European Respiratory Society Exacerbation Parameter Estimate
F	FEV1 FVC F or f FEV1/FVCx100 FEV1(% Pred)	Forced Expiratory Volume in One Second Forced Vital Capacity Females Forced expiratory ratio Forced expiratory volume in one second predicted for that age and sex Forced vital capacity predicted for that age and sex
G	GOLD	Global Initiative Of Obstructive Lung Disease
H	HR HRQL	Hazards Ratio Health Related Quality Of Life
I	ICP	integrated care pathway
J		
K	K-M KMSA	Kaplan Meier Kaplan Meier Survival Analysis
L	LVRS LREC Lower B LBM	Lung Volume Reduction Surgery Local Research Ethical Committee Lower Bound Lean Body Mass
M	MRC	Medical Research Council

Abbreviations

	MDI MID MOS MW test M or m	Mahler's Dyspnoea Index Minimally Important Difference Medical Outcomes Study Mann Whitney U Test males
N	NHP NICE	Nottingham Health Profile National Institute for Health and Clinical Excellence
O		
P	PEFR PCS Pred PCT PE % Pred Grip	Peak Expiratory Flow Rate Physical Component Score Predicted Primary Care Trust Parameter estimates Predicted grip of dominant hand for that age and sex
Q	QOL QWB	Quality Of Life Quality of Well Being
R	RCT ROC	randomised controlled trial Receiver Operating Curve
S	SGRQ SOLDQ SIP SF SD SE Sig SMWT SpO2 SRWQ	St. George's Respiratory Questionnaire Seattle Obstructive Lung Disease Questionnaire Sickness Impact Profile Short Forms Standard Deviation Standard Error Significant p value Six Minute Walk Test oxygen saturation Sunderland Respiratory Wellness Questionnaire
T	TPCT TDI Total Grip	Teaching Primary Care Trust Transitional Dyspnoea Index Right hand grip+ left hand grip
U	UCT Upper B UB URL	Urgent Care Team Upper Bound Upper Bound Uniform Resource Locator
V		
W	WHO	World Health Organization
X	XCOPD	Exacerbation of COPD
Y	yr or yrs	years
Z		

Chapter 1

INTRODUCTION

1.1 Chronic Obstructive Pulmonary Disease (COPD)

“COPD” refers to chronic obstructive pulmonary disease, a chronic disorder of the airways due to inflammation that leads to hypersecretion of mucus and/or destruction of the airways and alveoli in the lungs. These changes result in narrowing of the airways with the consequent airflow limitation causing breathlessness and ultimately disability (Department of Health and Human Services, 2010). Spirometry is the accepted method for measuring this obstruction to airflow (Gaensler, 1950 and 1951).

COPD is a complex disease with different phenotypes (Marsh et al., 2008). Around the age of forty years, people exposed to environmental air pollution especially cigarette smoke may experience a mild cough that produces clear sputum. During their middle to late 60s, shortness of breath with exertion becomes more evident and troublesome, especially if they continue smoking. Lower respiratory tract infections occur more often. As the severity of the disease progresses patients may become very breathless during infective exacerbations and sometimes require hospital admission (URL 1). Thus with continuing exposure to pollutants and/or recurrent exacerbations, the natural history is of disease progression (Viegi et al., 2007).

1.1.1 Diagnosis of COPD

COPD should be suspected in patients with a complaint of breathlessness or chronic cough with or without sputum production, especially if there is a history of exposure to tobacco smoke or other air pollutants (Raad et al., 2011, Rabe et al., 2007; Badgett et al., 1997). No single sign or symptom can adequately confirm or exclude the diagnosis of COPD (Holleman et al., 1995) although COPD rarely occurs under the age of 40 years. The presence of airflow obstruction should be confirmed by performing spirometry which currently represents the gold standard in COPD diagnosis. The severity is then classified using the degree of impairment of the forced expiratory volume in one second (FEV_1) (NICE, 2010).

1.1.2 Assessing the Natural History of COPD

Impairment of FEV₁ is seen as central to the progression of the disease. The Fletcher-Peto model (1976) is based on FEV₁ and was considered as the most comprehensive description of the natural history of COPD. However, only males were studied and this is a major drawback of the Fletcher-Peto model because today (30-40 years later) women represent about 50% of the COPD population (British Lung Foundation, 2005; Kohansal et al., 2009).

The airway damage in COPD is generally progressive and is linked to an increased inflammatory response of the lungs to harmful inhaled gases and particles, primarily from cigarette smoke however, various kinds of air pollutants are also commonly known to be risk factors for COPD (American Thoracic Society (ATS), 1995). In addition occupational exposure and indirect smoking (passive smoking) may play an important role in COPD occurrence, progression and exacerbation.

In COPD, the inflammatory response produces significant systemic consequences (Tkac et al., 2007; Huertas et al., 2011). These manifestations commonly include weight loss or obesity, reduced lean body mass with muscular weakness, osteoporosis and ischemic heart disease as direct effects and loss of appetite, anxiety and depression as indirect effects. These all lead to impairment in overall quality of life and health status (Cecere et al., 2011; Hynninen et al., 2007; Dourado et al., 2006; Agusti et al., 2003; Vandenberg et al., 1967). In more severe cases there may be circulatory and respiratory failure. These complications emphasize the necessity for the multidimensional approach to the assessment of the clinical impact of COPD.

1.2 Multidimensional Assessment of COPD Progression

A major advancement in understanding the natural history of COPD came in 2004 when Celli and colleagues (2004) presented data showing that their multidimensional grading system had a significant advantage over the Fletcher-Peto model. They established the BODE index (BODE – **B**MI, airflow **O**bstruction, subjective **D**yspnoea and **E**xercise test; a 10 point scale) (Celli, 2004) that proved to be a better predictor of the health outcomes than FEV₁ alone. More recently, Puhan and co-workers (2009) developed another multidimensional index (ADO) composed of **A**ge (**A**), Airway **O**bstruction (**O**) and MRC **D**yspnoea index (**D**). The index proved as useful as BODE for prognostic assessment in COPD patients.

Similarly Jones and colleagues (2009) developed the DOSE index that contains four COPD related measurements i.e. dyspnoea (D), airway obstruction (O), smoking status (S), and frequency of exacerbation (E). The index proved to be a simple tool to assess disease severity and future hospital admission events in patients with COPD.

1.2.1 Potential Drawbacks

Mobility is a very serious issue for an elderly population with COPD and Celli and colleagues (2004) only included patients who could carry out an exercise test. Soon after publication of Celli's paper, only one of six patients seen in a COPD clinic by Dr Niall Keaney (pers. comm., March 19, 2007) was capable of carrying out a meaningful exercise test.

Additionally, the exercise test is a time-consuming test which not only needs trained staff but also needs equipment and space which makes this test expensive in terms of resources required.

The ADO index used to evaluate Swiss and Spanish cohorts looked at 3 year mortality risk in these patients. By introducing age, the ADO index is compromised because age is the most important determinant of survival, independent of disease status and diagnosis. Therefore age has limited value in the stratification of a specific disease process (Celli et al., 2009).

Similarly, the DOSE index mainly focuses on markers related to health status, future events such as hospitalisation and respiratory failure and also disease management. However, this study did not take account of mortality which is one of the main COPD outcomes of interest both for patients as well as their health care providers.

A generally acceptable multidimensional index should be economical, easily measured in most clinical settings and applicable to all COPD patients. Furthermore, considering the chronic nature of COPD, there is a need to verify the efficacy of the index for assessing progression.

1.3 Modified Multidimensional Index to Assess COPD Progress

BODE is a validated but complex tool. In this study, the simpler BOD (which removes the exercise component from BODE) is presented and the pragmatic efficacy of BOD is explored.

1.3.1 Potential Drawbacks

The BOD index and other indices only cover physiological aspects of COPD. However, breathlessness (a marker of COPD progression and a component of BOD) is also associated with feelings of anxiety and/or depression, a recognised indirect comorbidity in these patients (Mikkelsen et al., 2004; Norwood et al., 2006; Janssen et al., 2010). Studies suggest that anxiety and depression may have an impact on COPD progression with outcomes such as hospitalisation, exacerbations and health status (Hynninen et al., 2010; Ng et al., 2007; Xu et al., 2008). However, anxiety and depression are potentially modifiable by changing and improving patients' attitude of mind (Hynninen et al., 2010). Health related quality of life (HRQL) is a relevant aspect of patients' perceptions and for COPD the St. George's Respiratory Questionnaire (SGRQ) (Jones et al., 1992) is widely used to assess health status. This is an illness questionnaire and does not represent the whole person including their attitudes to their illness. A need exists therefore, to explore wellness as a concept in COPD patients.

1.4 Psychological Markers of COPD Progression and COPD Outcome

It is a common perception that a patient's HRQL is vital to improve COPD outcome (Jones et al., 2002). However, there is a need to understand all the factors that are responsible for supporting the current health status (Daudey et al., 2010). This can be achieved by assessing the degree of wellness in patients with COPD. Wellness is a more recondite picture of health status.

Beneath the current state of health (HRQL) is lifestyle/behaviour, followed by psychological, mental stress and motivational levels. Deepest of all is the spiritual-being (Travis, 1970). A combination of all these levels indicates overall wellness status. This research has developed a wellness assessment questionnaire and applied this to study participants to investigate the role

of wellness in patients with COPD and its relationship to clinical status and health status of the disease.

1.5 Diagnostic Markers of COPD

Spirometry is a key for COPD diagnosis (GOLD, ERS/ATS, NICE) as is the electrocardiogram for myocardial infarction and blood pressure measurements for the diagnosis of hypertension. Spirometry can be used to monitor disease progression.

As FEV₁ is influenced by age, sex, height and ethnicity, it is best considered as a percentage of a predicted normal value. There are equations and reference normal values available in the literature (Crapo et al., 1990; Coultas et al., 1988; Glindmayer, 1995); with appropriate norms for local populations being used to assess COPD patients.

1.5.1 Potential Drawbacks

Impairment of FEV₁ is defined with reference to predicted values. Because predicted values are dependent on the size of the lungs, predictive equations must take into account the influence of height, gender, age and ethnic origin (Becklake et al., 1986). Of these variables, assessment of height is the one that may be subject to error although no predictive methodology deals with multi-ethnicity.

1.5.2 Examining an alternative Method of Measuring Height

Studies have also revealed that the prevalence of osteoporosis is increased in smokers (Cornuz et al., 1999; American Academy of Orthopaedic Surgeons, 2010) and this condition may reduce the actual height of COPD patients. Thus using the current height for predicted values of FEV₁ may mean that the degree impairment of FEV₁ is subject to confounding in an elderly population.

In the presence of spinal deformity, pulmonary function laboratories use arm span as a surrogate for height (Hepper et al., 1965; Golshan et al., 2007; Temple et al., 1988) and this measurement is not likely to be influenced by the presence of osteoporosis (Banik, 2011). The

present research investigates the relationships of armspan to measure current and historical height to further help calculating predicted FEV₁ in the diagnosis and classification of COPD. Overall, each and every biomedical researcher's ultimate aim is to overcome adverse consequences, reduce the burden, slow the progression, improve the quality of life, and prolong the lifespan of sufferers. These are factors that collectively help to build a more healthy society and the present study has made an attempt to explore further markers to improve health outcomes in patients with COPD.

1.6 Evaluation of Markers of Health Status in COPD

Several studies have proposed determinants that improve health status in patients with COPD. These well-established determinants of health status in COPD include age (Torres et al., 2006), gender (Ferrari et al., 2010), exacerbation frequency (Anzueto et al., 2009; Ansari et al., 2007), body mass index (Tsiligianni et al., 2011., Tsukino et al., 1996; Jampat et al., 2008), comorbidity (Yeo et al., 2006; Crisafulli et al., 2008) and multidimensional index BODE (Celli et al., 2004; Araujo et al., 2010; Casanova et al., 2011).

1.6.1 Potential Drawbacks

The above mentioned determinants play an important role in improving health status. However, considering COPD as a systemic condition, there are various other factors that need attention in order to provide improved information on the health status of patients with COPD.

1.6.2 Examination of new markers of Health Status

There are very few longitudinal studies looking at health status over time and the present study does this however it also examines potentially new determinants of health status in patients with COPD and compares data over time with already known determinants of health status. These include dyspnoea, handgrip strength and lean body mass. The present study also examines the relationship of new multidimensional indices of severity with health status (measured by SGRQ - St. George's Respiratory Questionnaire) in patients with COPD.

1.7 Haematological and Other Physical Marker of COPD Outcomes

C reactive protein (CRP) is generally used as a marker of acute inflammation in the body (Pasceri et al., 2000) and patients with COPD have an on-going inflammation. The present study examines the relationship of other physiological and psychological markers of COPD progression, health status and mortality with the degree of inflammation measured by high sensitivity CRP (hsCRP).

Long standing cough, breathlessness, and wheezing are common symptoms of COPD depending on how much of the lung has been damaged. Symptoms may suddenly get worse in cases of exacerbation. In this study, the duration of symptoms (in years), which has not been addressed previously, considered as a potential subjective measurement that may have an influence on COPD outcomes and this thesis explores the role of symptom duration in COPD outcomes.

1.8 Aims and Objectives of the Study

The main aim of this thesis is to chart the progression of chronic obstructive pulmonary disease (COPD) by a critical evaluation of current and newly developed markers. A novel multidimensional index has been used to describe the clinical impact of COPD and its natural history and progression over time. This research can then be utilized to help, improve, reduce, and control the devastating effect of this disease on patients' health with health care professionals targeting treatments to individual patients. Furthermore, this study can also be used to motivate these patients in order to improve their health status and wellbeing.

These aims have been achieved through the following objectives.

- ✓ A detailed and careful literature review of relevant studies.
- ✓ Identification and development of new markers that can be used to assess the severity of COPD and to monitor its progression.
- ✓ Data collection from the cohort of COPD patients.
- ✓ Interpretation of data obtained.
- ✓ Statistical analysis of data obtained.

- ✓ Clinical evaluation of a newly developed index “BOD” in predicting COPD outcomes.
- ✓ Critical review of other measures that can be used to improve BOD.
- ✓ Investigation of wellness status and its influence in COPD outcomes.
- ✓ Recommendations on the basis of results as to the best measures that can be used to predict COPD health outcomes.

1.9 Thesis Organization

Chapter 1 (Introduction) presents a brief background of the present study’s aims. Chapter 2 (Literature Review) contains a review of studies relevant to the aims of the thesis. In the next Chapter 3 (Methodology), detailed information about methodology and a brief account of statistical techniques and software used is given. Chapters 4, 5, and 6 discuss the critical evaluation of the BOD index, physical and psychological measurements, and haematological markers in detail on the basis of findings obtained. Chapter 7 (Discussion) reviews the key findings obtained, their interpretation, influence and significance in patients with COPD. The findings are compared with all other relevant studies in the literature. The closing Chapter 8 (Conclusion) summarizes the most important findings of the thesis and recommendations for future work that result from those findings.

LITERATURE REVIEW

2.1 Definition of COPD

Chronic Obstructive Pulmonary Disease (COPD) is a progressive disease (National Heart Lung and Blood Institute, 2010). It is defined as a preventable and treatable airflow limitation that significantly interferes with normal breathing and is not fully reversible (World Health Organisation (WHO, 2011); Global initiative of Obstructive Lung Disease (GOLD) 2010; Raheison & Girodet, 2009).

Classically COPD is comprised of two conditions; clinically defined “chronic bronchitis” and pathologically explained and radiologically diagnosed “emphysema” (National Heart Lung and Blood Institute., 2010). In some cases chronic asthma may be included under the umbrella of COPD (Figure 2.1). All of the above entities of COPD are highly influenced by smoking and other air pollutants.

Chronic Bronchitis is a clinical description of a symptom complex and is defined by hypersecretion, and a cough with mucoid sputum. There may be progression to narrowing of the medium sized airways (bronchi) as a result of the inflammatory response of the airways to smoke or other atmospheric pollutants (NICE, 2010). It is characterised by a loose wet cough that produces large amount of mucus.

Emphysema is characterized by abnormal dilatation of the distal airways and air sacs and may also be associated with a loss of elasticity in the lung tissue. The dilated air sacs (alveoli) are less supportive of the airways which tend to collapse during expiration resulting in air trapping (hyperinflation) (Snider et al., 1985; MacNee, 2005a).

In chronic asthma, airway remodelling and fibrosis occurs in the area surrounding the bronchioles due to a repeated process of inflammation (Bousquet et al., 2000).

According to WHO (2011) the COPD related terminologies 'chronic bronchitis' and 'emphysema' are no longer applicable in clinics. Both are now included within the COPD diagnosis.

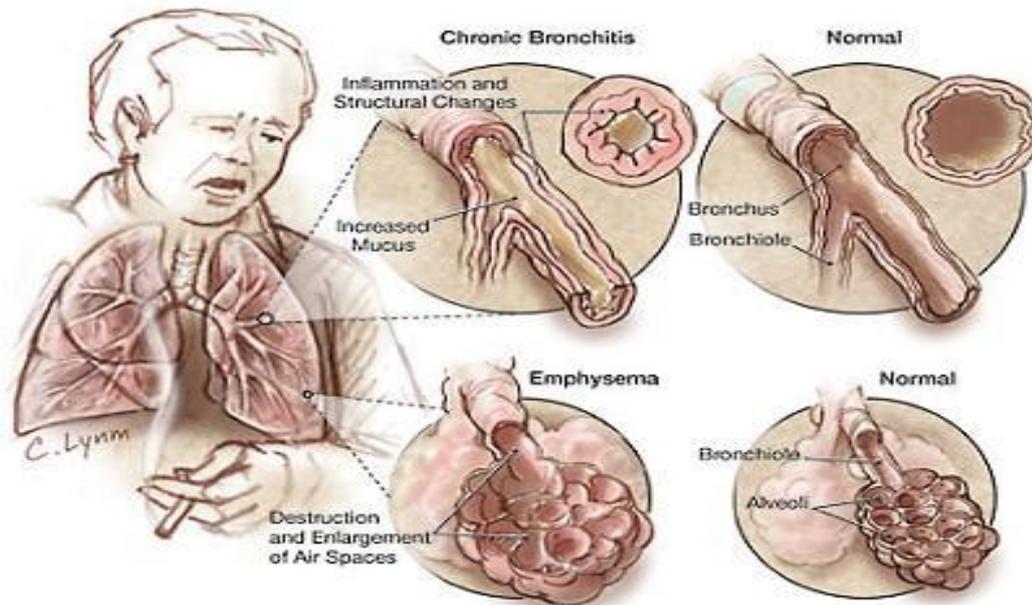


Figure 2.1. Anatomical view of COPD (URL 1)

2.2 History of COPD & Its Diagnosis.

The development of our understanding of COPD has continued for more than 250 years. A physical examination by stethoscope and the physiological measurement of lung capacity by spirometer, being the most widely used tools, for its assessment and diagnosis. Spirometry, however, is accepted as the most useful means for identification, screening, classification and monitoring the course of COPD before, during and after treatment (Petty, 2006).

Various attempts have been made to describe COPD. Bonet described emphysema as “voluminous lung” (Bonet, 1679). Later another scientist Morgagni studied 19 cases of emphysema and labelled it as “turgid lung” due to their air contents (Morgagni, 1769).

Badham (1814) was the first to use the collective terminology “Catarrh” for chronic cough and hypersecretion of mucus, a cardinal symptom of COPD and this is considered to be the first

major step in our clinical understanding of an important component of COPD; chronic bronchitis. According to Badham, chronic bronchitis and bronchiolitis are disabling disorders. Laennec, a famous clinician and pathologist who also invented the stethoscope, clearly described the emphysema component of COPD in his book “Treatise of diseases of the chest.” Laennec based his findings on careful dissections of patients he studied. He suggested that emphysematous lungs did not seem to be emptied well and were also hyperinflated (Laennec, 1834).

Smoking was very rare 200 years ago; however, emphysema may also occur in people who are non-smokers, particularly in people with a genetic predisposition (α_1 antitrypsin deficiency) or from factors in the environment (Laennec, 1834).

According to Laennec (1834)

“In opening the chest, it is not unusual to find that the lungs do not collapse, but they fill up the cavity completely on each side of the heart. When experienced, this will appear full of air The bronchus of the trachea is often at the same time a good deal filled with mucous fluid.”

Therefore, Laennec was the first to describe a combination of chronic bronchitis and emphysema.

Later, in 1846, the spirometer was invented by a scientist named John Hutchinson (Hutchinson, 1846). It now plays a key role in the diagnosis, classification, monitoring of progression and management of COPD. At that time Hutchinson’s instrument was only used to measure vital capacity. In 1947, Tiffeneau added the concept of timed vital capacity to measure airflow, which turned spirometry into a complete diagnostic device (Tiffeneau & Pinelli, 1947).

In the text book Osler’s Principles and Practices of Medicine (Osler, 1916) very little is mentioned about emphysema. The author believed that excessive pressure in the alveoli caused emphysema; however, he did not mention anything about spirometry and its role in COPD.

Based on Tiffeneau's work, Gaensler was the first to introduce the concept of the air velocity index and, later, the forced vital capacity (FVC), which became the foundation of the FEV₁ and FEV₁/FVC percent (Gaensler, 1950 and 1951) used today.

Ronald Christie who is one of the great clinicians of emphysema, suggested that "emphysema should be considered certain when dyspnoea on exertion, of insidious onset, not due to bronchospasm, or left ventricular failure, appears in a patient who has some physical signs of emphysema together with chronic bronchitis and asthma" (Christie 1944; p 145). Therefore, it is very obvious from Christie's statement that COPD has more than one component and thus history and physical examination is important for diagnosis. Oswald and co-workers (1953) studied 1000 cases of chronic bronchitis (Oswald et al., 1953) and explained the clinical features of COPD in more depth.

Dayman, who was a contributor to the book "Pulmonary Emphysema" (Barach & Bickerman, 1956), was the first to recognize the importance of spirometric and flow volume curve patterns in emphysema that are indicative of dynamic expiratory airway collapse. Menelee and Callaway were the pioneers who described the role of lung function tests in emphysema patients. Overall, there were 17 leading physicians and scientists who contributed to this classic volume of the 1950s.

There are two landmark meetings that were critical in the definition of COPD: The CIBA Guest Symposium (Ciba Guest Symposium, 1959; Donald, 1971) and the American Thoracic Society (ATS) Committee on Diagnostic Standards (Committee on Diagnostic Standards for Non Tuberculous Respiratory Diseases, 1962) respectively. According to ATS "chronic bronchitis in clinical terms is a chronic cough lasting for at least three months over a two year period". On the other hand ATS defined emphysema in anatomic terms as an enlargement of alveolar spaces and loss of alveolar walls. Neither of the definitions considers physiological measurement as a part of the definition. Asthma was described as a state of airway hyperresponsiveness to a variety of stimuli and asthmatic bronchitis was considered an overlapping condition (Committee on Diagnostic Standards for Nontuberculous Respiratory Diseases, 1962). Many other attempts have been made to define COPD. However, neither of them has improved these basic definitions. The only improvement made is that COPD is now defined in functional terms.

William Briscoe is believed to be the very first person to use the term “COPD” in the meeting discussion at the 9th Aspen Emphysema Conference. This term became established and today we refer to COPD as the designation of this growing health problem (Briscoe & Nash, 1965).

2.3 PATHOGENESIS OF COPD

In 1968, Hogg and colleagues suggested that the major site of increased airway resistance is the airways that are situated peripherally, in the lungs of smokers, with airflow limitation, i.e. bronchi and bronchioles of < 2 mm in diameter. Another study suggested that hematopoietic cells including macrophages, lymphocytes, and neutrophils play vital roles in the pathogenesis of COPD (Spurzem et al., 2005).

Asthma, chronic bronchitis and emphysema are all characterized by the presence of airflow obstruction. Distinguishing between these diseases is difficult and may be impossible; the Venn diagram below (Figure 2.2) suggests that overlap syndromes occur (ATS, 1995).

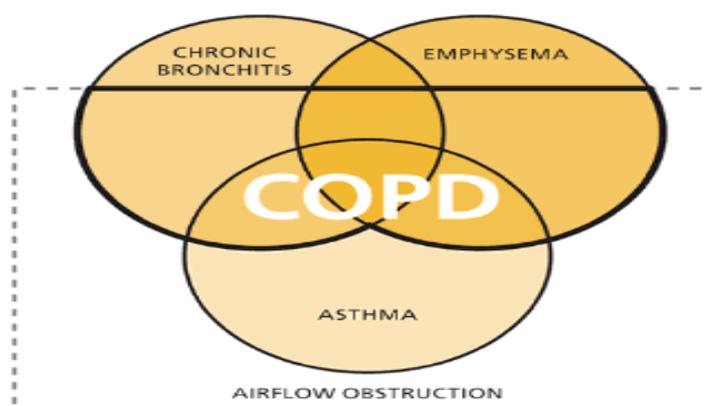


Figure 2.2. Venn diagram shows overlapping clinical conditions (URL 2)

2.3.1 Progression from Other Respiratory Illnesses

In this regard, there are two major concepts that seek to explain COPD pathogenesis; the Dutch hypothesis and the British hypothesis. Orié and his team put forward a concept of genetically influenced hypersensitivity of bronchial airways in COPD (Orié and Sluiter, 1960). They also

suggested that the various forms of airflow obstruction are different expressions of a single disease entity and introduced a term called “chronic non-specific lung disease” (CNSLD). On the other hand, the British hypothesis (Stuart-Harris et al., 1953; Scadding, 1959) stated that air pollution and repeated chest infections are the main causes that contributed to the pathogenesis and progression of the disease.

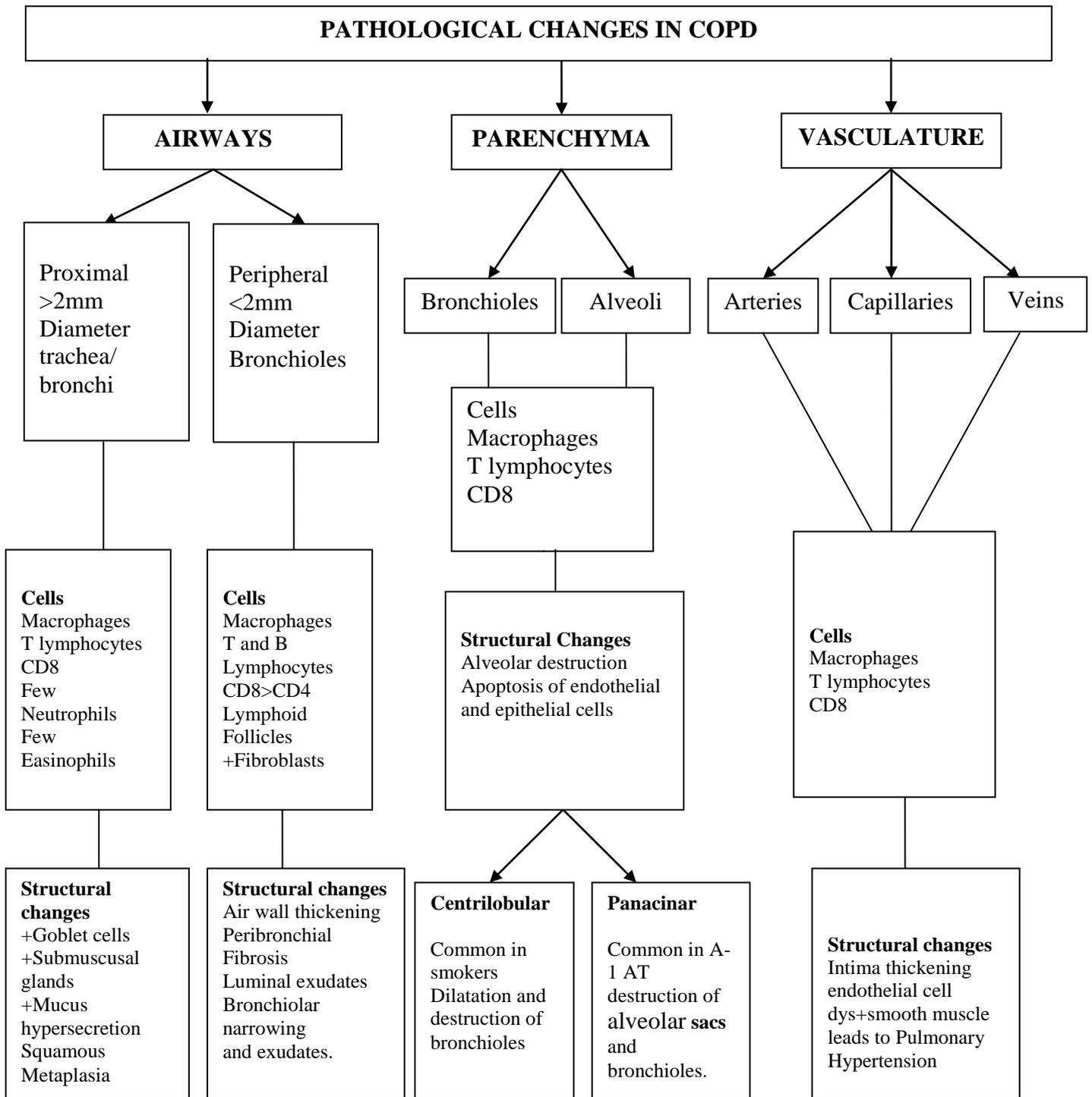


Figure 2.3. A summary of the pathological changes that occur in COPD Lungs (Adapted from: Hogg et al., 1968; Saetta et al., 2000; Torato et al., 2001)

However, both hypotheses are probably acceptable as studies have suggested that bronchial hyperactivity, irritant exposure and chest infections all play important roles in the pathogenesis of COPD. Figure 2.3 summarizes the pathological changes that occur in COPD.

2.4 Factors Influencing the Pathogenesis and Progression of COPD.

Although COPD is known to be a preventable and a treatable condition, the airflow limitation that occurs in COPD is not completely reversible (Pauwels et al., 2001; Celli et al., 2004). The most important cause of COPD in the world is cigarette smoking (Churg et al., 2008; Jordan et al., 2011; Mannino et al., 2007). In some individuals environmental and occupational exposures to fumes, gases, vapours and dust are the major risk factor (Trupin et al., 2003). Additionally exposure to domestic or biomass smoke (Guoping et al., 2010; Smith et al., 2003; Kiraz et al., 2003), malnutrition (Bargon & Muller, 2001; Ferreira et al., 2000), childhood infection (Shaheen et al., 1995), genetic predisposition (Lomas and Silverman., 2001), hyperresponsiveness of the airways and asthma (Scichilone et al., 2006) are also regarded as important causes of COPD particularly in the developing world i.e. the regions where cigarette smoking is less prevalent. Some important exposures (Smith et al., 2003) that influence COPD progression are presented in figure 2.4.

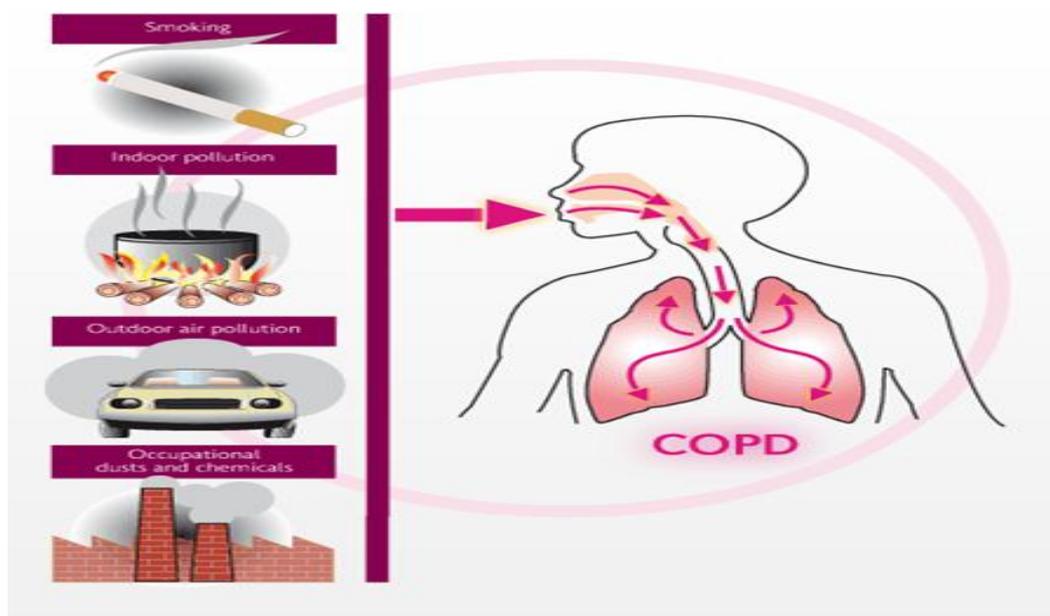


Figure 2.4. Risk factors of chronic obstructive pulmonary disease (URL 3)
(Adapted from GOLD 2009)

2.4.1 Smoking and COPD

Smoking is the major cause of both development and poor outcomes in patients with COPD due to its influence on the progression of COPD in individuals irrespective of their smoking status. Non-smokers are defined as subjects who have not smoked 100 cigarettes in their life time. Disease progression may also differ in patients with different smoking status; however, it has been suggested that complete smoking cessation may be beneficial even in older and more advanced COPD patients (Zielinski et al., 2010).

There are various observed and published articles which confirm the association of smoking status with disease severity, progression, and mortality (Fletcher and Peto, 1977). One study showed that COPD patients who continue smoking have a significantly impaired health related quality of life (HRQL) as compared to those who stop smoking (Prigatano et al., 1984). On the other hand, current smoking has been associated with better HRQL in the study by Wijnhoven and colleagues (2001). The explanation given was that subjects who do not stop smoking might be those with a less severe stage of the disease and therefore less health status impairment. The present study also examines the effect of both active and passive smoke on disease progression.

It has been also suggested that an undefined genetic makeup of heavy smokers may minimize or maximize the chances of developing COPD in later life. The gene ADAM33 has been connected with asthma and studies suggest that patients with asthma and emphysema (a permanent dilatation of the air sacs of the lungs accompanied by destruction and loss of elasticity alveolar walls) are more prone to develop COPD if they smoke (Sadeghnejad et al., 2009).

2.4.2 Tobacco Smoke (Passive Smoking)

Passive smoke (also called second hand smoke) is smoke that mainly comes from two different sources -- mainstream smoke or indirect cigarette smoke which is exhaled by an individual during smoking, and a side stream smoke or a direct smoke emitted directly from the end of a burning cigarette (Leader, 2008; Coultas, 1998). Studies have suggested that both types contain the same toxic substances (US Department of Health, 2006; Oberg et al., 2010).

Studies have also confirmed that tobacco smoke is one of the major sources of indoor pollution both in developed and developing countries. PM_{2.5} which is a small particle emitted from combustion, including cigarette smoking, has a substantial effect on deaths/year. According to a UK Government report, a 6% increase in death rate occurred in western European and North American populations after a modest increase in the ambient annual average level of PM_{2.5} of about 10micrograms /m³. Where solid domestic fuel combustion is common concentrations can easily be raised by this amount (Department of Health, UK, 2005). It is also indicated that before the smoking ban in Irish workplaces, fine particulate pollution, PM_{2.5} levels in Dublin restaurants and pubs were almost 6 times higher than in the outdoor environment (Goodman et al., 2007). This later decreased by 84% when the smoking ban came into effect. This strongly suggests that second hand smoke is the major indoor source of PM_{2.5}. Eisner and colleagues (2006) have studied the direct impact of second hand smoke on health outcomes and showed that the highest tertile of urine cotinine in COPD patients was longitudinally associated with severe dyspnoea, COPD severity, and a worsening of health status in these patients (Eisner et al., 2006).

Elastin, a fibrous protein is a target for injury in COPD and plays an important role in pathogenesis of COPD (Deslee et al., 2009) and a recent study (Slowik et al., 2011) suggests that a degradation of body elastin occurred in lungs due to second-hand smoke exposure which possibly leads to lung structure damage resulting in the development of COPD.

The above discussion of the global burden of disease attributable to second-hand smoke suggests that in order to achieve substantial health improvements, attempts should be made by extensive and effective public health programmes, awareness and clinical interventions to reduce and to avoid passive smoking worldwide.

2.4.3 Exposure to Other Pollutants (Mainly Air, Occupational & Environmental)

The airway obstruction in COPD is generally progressive and is linked with an abnormal inflammatory response of the lungs to harmful gaseous particles and primarily to cigarette smoke. Because various kinds of air pollutants are commonly known as risk factors for COPD (ATS, 1995), it appears that occupation and indirect smoke (maybe passive smoke) are likely to play an important role in COPD occurrence, progression and complication.

Environmental air pollution is another factor that influences both the development and progression of COPD (Blanc et al., 2004, Trupin et al., 2003). But there may be other causes such as in-house smoke released from biomass fuel (wood) used for cooking purpose (Osman et al., 2007) and this is becoming an increasing problem in third world countries. Another study suggested that both indoor and outdoor exposure to air pollutants may exacerbate COPD (Liu et al., 2008) and thus influence outcomes.

Occupational and environmental exposure to chemicals found in the environment may potentiate or aggravate the inflammatory effect in the lung airways of COPD patients (Meldrum et al., 2005; Christiani, 2003). There is a possibility that heavy smokers and non-smokers who are not exposed to such pollutants exhibit no pathological changes in the airways and are relatively safe. Lastly, there are varieties of cigarettes available in the market with different brand names and there may be some specific brands that are responsible for COPD. To date, such substances are not known. Substances including Beedi, Cigar, Hookah and Pipe that are common in some parts of the world may be responsible for the development of COPD (Malik 1977; Jindal et al., 2006). Biomass burning in both rural and urban habitations may affect both men and women (Torres et al., 2008; Tan et al., 2008) and could lead to the development of chronic lung disease later in life.

The use of biomass substances for cooking and heating is a major source of indoor pollution in the developing world. This smoke contains high levels of organic chemicals released into spaces that are poorly ventilated, particularly in developing and poorer countries. However, evidence-based findings are needed to draw any final conclusion. Therefore there is a need to investigate its effects on patients with established obstructive lung disease including its impact of lung function impairment and on the clinical course of obstructive pulmonary disease (Eisner et al., 2007) particularly in developing countries.

In addition, Osman and co-workers (2007) have suggested that nitrogen dioxide (NO₂) another major indoor pollutant yielded from combustion, during the operation of gas heaters or gas stoves may be associated with COPD. However, it is also suggested that NO₂ exposure is not consistently associated with worsening respiratory symptoms or lung function impairment (Eisner et al., 2002, Jarvis et al., 1998, Moran et al., 1999, Blance et al., 2005). Therefore, further research will be needed to explore the influence of indoor NO₂ on pulmonary function

(Lagorio et al., 2006). On a global scale, a large burden of obstructive lung disease symptoms is attributable to indoor combustion (Ramirez-Venegas et al., 2006).

It has been documented that occupational exposure to some substances such as silica and cadmium also increase the risk of COPD. Occupational related exposure in coal miners, construction workers, metal workers, motor mechanics, cotton workers and shipyard workers have also been reported as factors (Hendrick, 1996; Boschetto et al., 2006) that potentiate the adverse events related to COPD including worsening of symptoms, hospitalisation and disability.

2.4.4 Family and Genetic Predisposition

Deficiency of alpha-1-antitrypsin is the only known genetic factor that is widely accepted to predispose both smokers and non-smokers to COPD (Lomas and Silverman, 2006). Damage to peripheral airways and alveoli is thought to occur when there is an imbalance between proteinases (e.g. elastase from polymorphonuclear neutrophils) and anti-proteinases (α_1 antitrypsin being the most important). Alpha₁ antitrypsin deficiency is a recessive disorder with prevalence in the UK estimated higher than other European countries (Hutchinson, 1998; Blanco et al., 2006). It is important to screen these individuals at birth as recurrent lower respiratory tract infections and cigarette smoking accelerate the development of emphysema.

Studies also suggest that some single nucleotide polymorphisms (SNPs)-human DNA sequence variations are more common in COPD sufferers who smoke than in smokers without COPD (van Diemen et al., 2005). Patients with a family history of respiratory problems (suggestive of parental emphysema, asthma, autoimmune disease, any genetic defect or COPD sensitivity), a past history of recurrent chest infections and childhood asthma are more prone to develop COPD later in life, which can be earlier and more severe in those who smoke. Some studies have also suggested that tobacco expressed as pack years correlates weakly with FEV₁ (Marcus et al., 1988; Sadeghnejad et al., 2007).

2.4.5 Gender and COPD

Gender plays an important role in the development of COPD. Generally, COPD is more prevalent in males, and this may be the result of smoking habits and occupational exposure to certain chemicals. However, during the last decade the prevalence of smoking has increased among women and some evidence suggests that women are more prone to damage their lung function than men (Chapman et al., 2001).

COPD in non-smoking females is more prevalent than in non-smoking males and this may be explained by the difference in size of their lungs (Sorheim et al., 2010). Female lungs are smaller than male lungs and the smaller cross-sectional dimensions of the airways may contribute to airflow limitation. This accords with Poiseuille's law where resistance in a tube is proportional to the fourth power of the radius.

Many studies have highlighted the importance of gender in chronic diseases and its relationship with mortality (de Torres et al., 2009). It is also suggested that frequent exacerbations are more prevalent in females than men. Women are also at a higher risk of malnutrition (Leader, 2011). Furthermore, the data of the Rotterdam Study that addresses the important issue of a remarkably high incidence of COPD in young women, suggests a further shift toward females in the sex distribution of COPD (van Durme et al., 2009). However, despite this inconsistency in the gender predominance, mortality remains higher in males (de Torres et al., 2009).

In relation to HRQL in COPD, lower HRQL among women has been widely described (Belloch et al., 2003, de Torres et al., 2005 and 2006). It remains unclear whether this is due to differential reporting patterns, or whether there is a real difference in their health status.

Gender is therefore important for COPD susceptibility and progression (Kirkpatrick et al., 2009).

2.4.6 Age and COPD

As with most chronic diseases, the prevalence of COPD is strongly associated with age (Halbert et al., 2006). This is one of the most important personal characteristics known to have an impact on progression, health, mortality and morbidity. Data collected in a general Italian population showed a progressive increase of the prevalence of chronic bronchitis and emphysema with age in both genders (Viegi, 2001).

Blake and his co-workers reported that ageing is related to the decline in health related quality of life (HRQL) especially in its physical aspects (Blake et al., 2000), which could lead to disability and death.

2.4.7 Body weight and Body Mass Index in COPD

The phenomena of loss of weight together with muscle weakness and loss of muscle mass in patients with COPD are not clear. However, experts (GOLD, 2009) have suggested a number of factors that potentially cause loss of weight and muscle tissue which, in turn, influences progression and assessment in these patients (Bargon et al., 2004).

These factors may include:

- Breathing and any other physical activity in these patients requires more energy thus more nutrients are needed to produce more energy.
- Drugs such as oral corticosteroids may be needed as a treatment option and may influence the breakdown of muscle tissue.
- Loss of appetite as they feel depressed due to their breathing symptoms. Additionally, some drugs used to treat depression may cause loss of interest in food (Chavannes et al., 2005).
- These patients have less oxygen available to diffuse into the blood which affects the ability of the body to metabolize food properly.
- Postprandial (after eating) effect on breathing, as a full stomach may exert pressure on the diaphragm (muscular partition between thorax and abdomen that supports lungs and helps breathing) therefore, make it difficult to breathe (Palmer and Hiimae, 2003). Furthermore, chewing or swallowing of food, particularly solid food requires breath

holding which may not be comfortable, particularly if the patient has breathing difficulties.

- COPD patients are generally elderly and live alone or with a carer (Pinnock et al., 2011). Therefore, they may not take in quality food or balance their diet on time. This is especially true for those who belong to a limited income group as this potentiates poor eating habits.

If patients with COPD lose weight e.g. when fat free mass (FFM) falls below 16 kg/m^2 or the body mass index (BMI) falls below 21, increased mortality has been found (Marti et al., 2006). So, in addition to FEV_1 , BMI has proved useful in predicting outcomes, such as survival, and several authors have recommended that it should be evaluated in all patients (Schols, 1998; Landbo, 1999). BMI is an easily measured index calculated by dividing total body weight (in kg) by height squared (in m^2). A value of less than 25 kg/m^2 is associated with increased mortality (Marti et al., 2006; Yang et al., 2010).

Patients with COPD who demonstrate a significant weight loss do not only have a worse prognosis but also develop peripheral muscle weakness (Arora and Rochester, 1982). This leads to exercise limitation and health impairment (Vandenbergh et al., 1967; Dowson et al., 2001) and these factors act as an important cause of disability. Chen and colleagues (2000) found that a $\text{BMI} < 20$ and a $\text{BMI} \geq 28$ among male and female subjects respectively were associated with an increased prevalence of COPD. De Angelis (2001) reported hypercapnia during sleep in COPD patients with a high BMI (De Angelis et al., 2001). Later studies documented that men with a low BMI are at an increased risk of developing COPD (Raida et al., 2002). Another interesting study carried out by Guerra and co-workers (2002) concluded that patients with chronic bronchitis are more likely to be obese whilst patients with emphysema are underweight.

Thus, until 2002, studies have documented the prognostic value of low and high body weight in patients with COPD as well as in the general population. However, it was unclear whether low body weight is a risk factor for COPD or a consequence of the disease. But, research carried out by Gronberg and co-workers (2005) concluded that dietary problems are common in the group studied, and related to smoking habits and gender. Chavannes and his team (2005) suggest that, in primary care, depressive symptoms in COPD seem to be related with female

gender, high BMI and dyspnoea. Patients with COPD have a high metabolic rate that is not balanced by high dietary intake, and thus results in low body weight.

2.4.8 Life style and COPD

Lifestyle is also an important factor and this varies in different parts of the world. If we consider western society, smoking is common in males and hence their female partners are exposed to passive smoke (Gupta et al., 2002).

Another study suggested that culture and ethnic origins may also influence COPD progression and should be investigated further (Siu et al., 2009).

Education is important in the sense that education leads to people becoming aware of general symptoms and how and when to seek medical advice. Thus earlier diagnosis can prevent disease progression.

Smoking marijuana and opium may be a precipitating factor for airway inflammation as well as air pollution and this is seen across the world (Tan et al., 2009). Psychosocial and economic status may be related to the use of these addictive substances (Leader, 2008). But there is an uncertainty regarding its impact on progression in patients with COPD and this area needs further attention particularly in developing and poor income countries where the addiction to these drugs are more common.

Furthermore, significant social and occupational inequalities are found in men between 20-64 years of age. Those engaged in unskilled manual occupations are at more risk (14 times) of dying from COPD than those involved in professional occupations (BTS, 2006).

Thus at a personal level, each individual has specific risk factors influencing progression of the disease based on economic conditions, psychosocial status, attitude towards disease management and improved health, work related exposure, family and life time medical and drug history. The present study will evaluate some of these markers and their role in COPD progression.

2.4.9 Low Socioeconomic Status and COPD

The association of a high prevalence of COPD with low socioeconomic status has been reported in many epidemiological surveys (Thorn et al., 2007; Eisner et al., 2011). Economic difficulties have also been identified as a marker of poor disease course (Antonelli-Incalzi et al., 2007). It has also been found that with patients aged 70 years or above hospitalisation due to exacerbations are more prevalent (Antonelli-Incalzi et al., 2007).

Populations of poor countries are exposed to indoor air pollutants that result from the combustion of solid fuels in poorly ventilated work or living spaces, which significantly influence the burden of COPD-related diseases, particularly in (non-smoking) women (Liu et al., 2008). However, preventive strategies may vary between countries that particularly need to improve air-cleaning technology, air quality legislation and information dissemination together with greater provision and installation of improved cooking stoves. Therefore a co-operative effort is needed from both governments and society to improve COPD related outcomes.

In low income countries, both the amount of food and quality of the diet is influenced by income, which may lead to malnutrition or insufficient nutrients. One study has suggested that poor socioeconomic status plays an important role in the development, progression and other life threatening manifestations of COPD (Tan and Ng, 2008). Moreover, sufferers do not consult a physician because they neither have the money to pay the doctors nor to buy prescribed medicines. It also appears that diet influences self-immunity (e.g. antioxidants) (Nelson, 2009) and thus delays inflammatory responses to certain inhaled substances.

Clinically, a viral infection (mainly adenovirus) within the lungs heightens inflammation and hyperactivity of the bronchial passages but the role of viruses in the pathogenesis of COPD remains controversial. Nevertheless, it has been proposed that childhood respiratory symptoms and a history of recurrent respiratory infection could lead to COPD in adulthood (Barker et al., 1991, Shaheen et al., 1994, Sethi, 2000, GOLD, 2004).

Irrespective of gender and age, there are several other proposed risk factors. These risk factors include gestational age, weight at birth, smoking and smoke exposure from both mother and father throughout gestation and several other irritants throughout adulthood. Family history may also be important to rule out chances of airway disease development. Additionally, the

body's self and autoimmune response to certain chemicals may be of relative importance suggesting an autoimmune nature of COPD (Nunez et al., 2010). Several studies also suggest that, irrespective of smoking status, older patients with a low BMI are statistically associated with COPD. In both factors, education and poverty have a role.

Moreover, epidemiological studies have played an important role in the characterization of the disease at a population level, pointing to potential causes and assessing its impact on the patient, individually and on the society collectively. But more research is needed to explore factors that influence progression that in turn, could lead to more comprehensive strategies to overcome poor outcomes in these patients.

2.5 COPD Outcomes

COPD is one of the major causes of preventable disability and death. In the UK, COPD is the 2nd commonest condition for emergency hospital visits and the 5th commonest cause of hospital readmission. Thus COPD becomes very costly both for patients as well as for health care providers (Department of Health, UK, 2010).

The chronic, progressive and irreversible nature of COPD will lead to outcomes that impact upon both patients with COPD as well as their care providers.

2.5.1 Mortality

COPD causes approximately 26,000 deaths every year in England and kills more females than breast cancer and more men than prostate cancer (Royal College of Physicians of London, British Thoracic Society (BTS) and British Lung Foundation (BLF), 2008).

Worldwide, at least 2.5 million deaths from COPD were recorded in 2000 and approximately half were in the Western Pacific Region especially China. In the United States, COPD causes death to someone every 4 minutes (COPD Foundation, 2008). Furthermore, 12 million people have diagnoses of COPD, and it is estimated that 2 million cases still remained undiagnosed (NHLB, 2009). In other industrialized countries more deaths due to COPD occur and the regional prevalence of COPD in adults varied from 0.5% in parts of Africa to 3–4% in North America in 2000 (Lopez et al., 2006). More recently, the mortality data published by General

Register Office of Scotland (GROS) indicates that the annual number of deaths due to COPD in males fell from 79-52 per 100,000 to 34% between 1981 and 2006 and increased from 21.2 to 40.9 to 93% in females (Scottish Public Health Observatory, 2011). In the UK, annually, approximately thirty thousand people die of COPD and the majority of those are aged over 65 years (Britton et al., 2003). People dying from other diseases (cardiovascular, lung malignancy) often have COPD as a comorbid condition (Hansell et al., 2003). COPD related mortality also shows a strong rural and urban gradient (Eberhardt et al., 2001) especially in the Northern part of England (Hansell et al., 2003).

Mortality in severe COPD due to acute exacerbation of COPD ranges from 36%-59% and this compares unfavourably with cancer patients; 'the 5-year relative survival rate for persons diagnosed with cancer is 62.7%, with variation according to cancer site and stage at the time of diagnosis' (Gloeckler et al., 2003).

In the UK, pulmonary pathologies are the third commonest cause of chronic sickness in the working age population (aged 45-64 years). In contrast to cardiovascular and other chronic illnesses, deaths from COPD are predicted to rise substantially as reported by Center for Disease Control (CDS) in 2008 (COPD Alert Fact Sheet, 2010) (Figure 2.5).

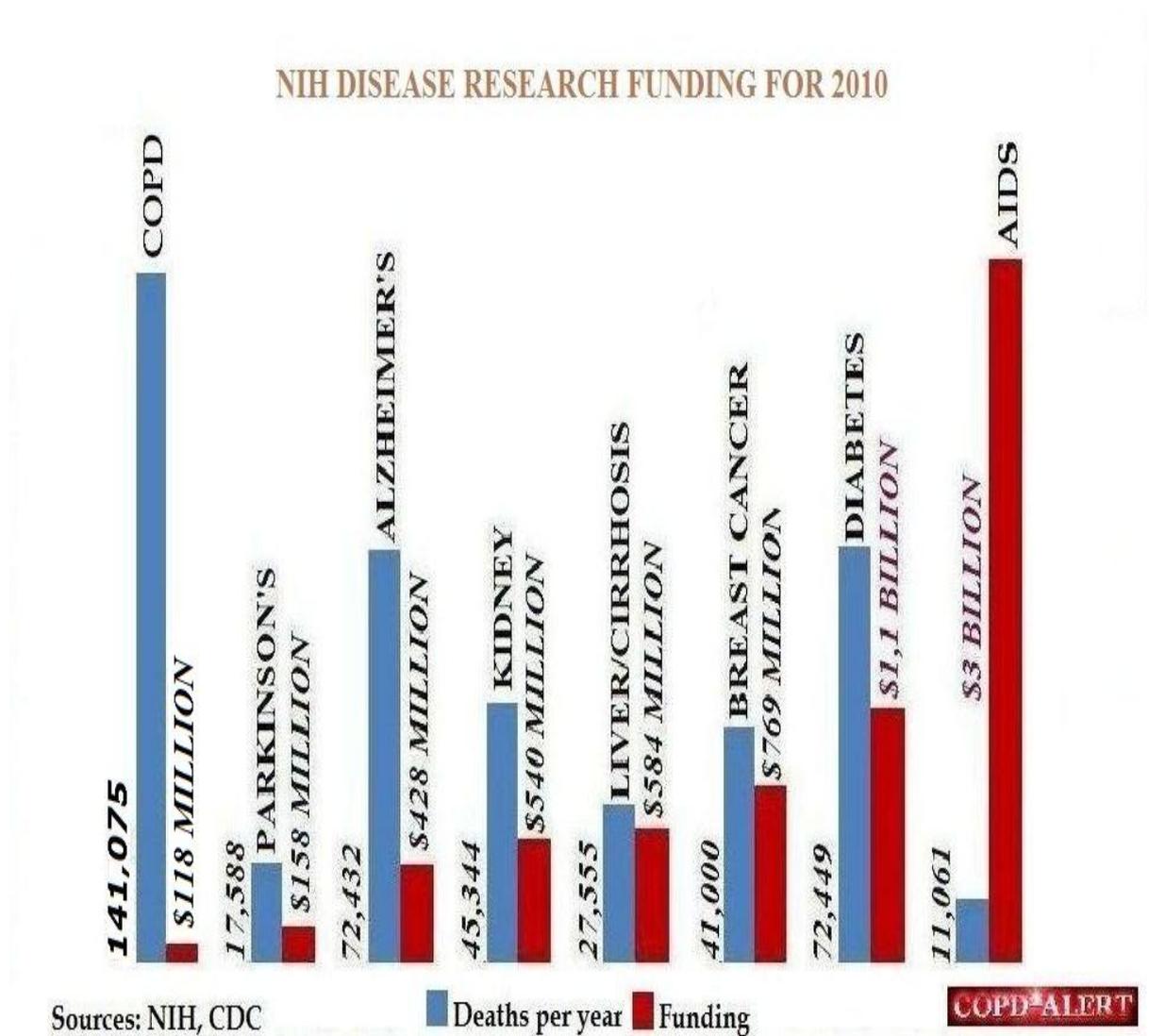


Figure 2.5. Mortality trends of different chronic illnesses in the US (URL 4)

2.5.2 Exacerbations

Exacerbation, which is defined as a worsening of the severity of the disease or its signs and symptoms, is very common even in mild stages of disease (Hurst et al., 2010). The recurrent attacks are caused by smoking or infection and often require emergency (hospital at home or hospital care) treatment (BTS Guideline Development Group, 2007) and in a significant proportion of patients may lead to respiratory failure.

2.5.3 Impaired Quality of Life

Health status impairment is also common in these patients. Considering a chronic illness and long standing breathlessness, functional impairment is also common even in those with a mild stage of the disease (Miravittles et al., 2009).

2.5.4 Co-morbidities

Comorbidities are also common in patients with different stages of COPD (Feary et al., 2010; European Lung Foundation, 2011). These patients are at higher risk of premature disability and death from cardiovascular causes and stroke. More importantly, deaths in patient with a milder form of COPD are more likely due to other associated comorbid conditions than the COPD itself (Feary et al., 2010).

2.5.5 Anxiety and Depression

The prevalence of anxiety and depression are very common in patients with COPD. This psychological condition can have a significant impact not only on patients, but also on their families, carers, society, and the ultimately the progression of the disease (Maurer et al., 2008) due to its influence on treatment adherence, disturbed sleep and appetite and self-care.

Therefore, the key reasons for the poor outcomes seen in patients with COPD are poor symptom recognition, late diagnosis of COPD and insufficient or maybe inappropriate methods of assessment of its progression and management and further research should be carried out to overcome the overwhelming burden of the disease and its outcomes.

2.6 Complexities in the Progression of COPD

It has been suggested by Mannino and co-workers (2000) that COPD is usually in the moderate to severe stage by the time clinical signs become obvious and the patient seeks medical advice (Mannino et al., 2000).

COPD is a very complex and heterogeneous disease with various clinical presentations (Nishimura et al., 2012; Decramer et al., 2008; Pistolesi et al., 2010). In the early stages of

COPD, patients appear to be symptomless and may not visit a physician until the condition becomes worse and reaches an advanced stage (Van Schayck et al., 2000; Clotet et al., 2004). Around the age of 40, people with COPD experience a mild cough with or without sputum. During their middle to late 60s, shortness of breath on exertion becomes more troublesome, specifically if they continue smoking. There are a number of reasons for this delay in the appearance of symptoms (Celli et al., 2004). Firstly there may be no sudden episodes of chest symptoms such as chest tightness, breathlessness, cough and/or wheeze that might alert the patient, as occurs in patients with asthma (Van den Boom et al., 1998). Secondly, a delay in recognition of the true impact of COPD might occur because the disease usually develops at that time of life when people generally begin to modify their leisure and recreational activity to less strenuous pursuits. Therefore, we can assume that a damaging process has been started long before the time when a patient usually seeks medical advice for their symptoms.

Pneumonia and other lung infections occur more often as the disease advances. In severe stages, patients become short of breath even at rest and/or modest activity, which sometimes requires a course of antibiotics and/or steroids possibly with hospital admission (Bahadori et al., 2009).

Patients with COPD particularly in severe cases often complain of disturbed sleep (Omachi et al., 2010) because they are unable to breathe easily in a lying down position therefore they sleep in a semi-sitting position or need to sit up to cough (Omachi et al., 2010).

COPD also presents with various kind of both pulmonary and extra-pulmonary manifestations. These manifestations commonly include weight loss, loss of appetite, anxiety, depression, osteoporosis, cardiovascular problems and finally lead to impairment in overall quality of life and health status (Dourado et al., 2006; Barnes et al., 2008; Smith, 2009). In most severe cases, it may lead to circulatory and respiratory failure. This emphasizes the necessity for comprehensive monitoring and assessment of all the aspects of disease progression in patients with COPD and to utilize a multidimensional approach to assess these patients.

If COPD is allowed to progress there are more hospitalisations and unscheduled visits to emergency departments or GP surgeries. These are all expensive and will require medication and other expensive interventions to manage these COPD related consequences. There is also a societal cost in terms of patients' restricting their leisure activities and dropping out of the

work force. This burden may be lessened if the condition is diagnosed earlier and monitored effectively.

A patient –centred, and evidenced based report published recently (2010) by the Department of Health (DH), England) is a very comprehensive document which recognises that potentially there are substantial gaps with respect to COPD disease management. They recognise that there is significant scope for improvement in the prevention, diagnosis, management and assessment of progression of COPD, and propose a fundamentally new approach to reducing the COPD burden (Kearney et al., 2010).

However, identifying and filling those gaps could play a vital role in driving up quality and delivering significantly better outcomes in these patients.

2.7 Measurement and Assessment of Progression (Natural History) & Severity of COPD

Studies suggest that the natural progression and history of COPD involves very complex cellular, microbiological and biochemical events in the small airways and adjacent alveoli which may lead to loss of elastic recoil (Saetta et al., 1997 & 2000; Petty et al., 1987). As a result, the lungs enlarge but the airways become narrower leading to early spirometric airflow limitation (Burrow et al., 1987).

Therefore, it is essential to understand the development of healthy and diseased lungs with aging and also the gender related differences that may be associated with pulmonary impairment in order to plan strategies to monitor and treat different lung pathologies such as COPD (Cosio & Agusti, 2010).

The Fletcher-Peto model (1976) explains the natural history of COPD and uses an FEV₁ based model to describe the natural history of COPD (in males) (Fletcher & Peto 1977). This finding is the most important finding in the field of COPD as it established the impact of smoking on COPD and significance of smoking cessation at different stages of COPD (Anthonisen et al., 1994). This model demonstrates that lung function declined progressively over time and that the rate of decline is associated with ageing (Figure 2.6). This study also showed a slower rate

of FEV₁ decline in non-smokers and, surprisingly, many smokers who seemed highly resistant to be influenced by adverse effects of smoking on their lungs. In contrast, there are smokers who are susceptible to lose FEV₁ at faster rate and are highly prone to develop clinically significant obstruction of the airways. It was also found that in smokers who stop smoking (exsmokers), the expected rate of lung function decline may revert to normal. Fletcher and Peto concluded that both hypersecretion of mucus and bronchial infections does not influence lung function deterioration. That concluding remark from Fletcher and Peto made development and progression of COPD more controversial and the subject become the focus of all investigations regarding disease progression.

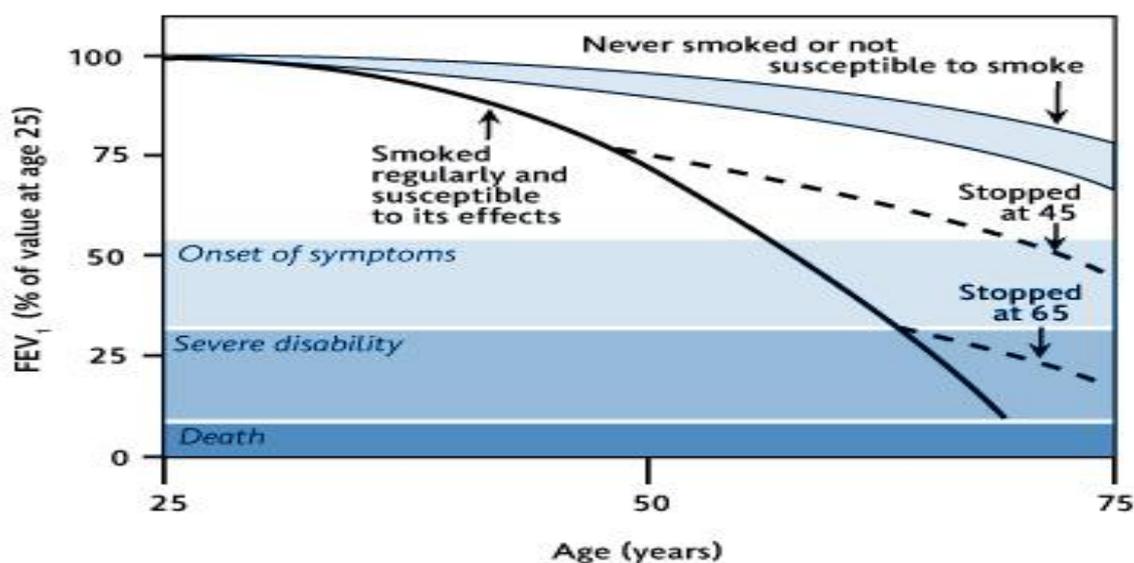


Figure 2.6. Fletcher–Peto Curve indicating effect of smoking by age on lung functions
(Adapted from Fletcher Peto, 1977) (URL 5)

More recently (Kohansal et al., 2009) revisited with a larger cohort consisting of both males and females for the first time. They were followed up for 23 years and put forward some novel findings related to the natural history and progression of COPD. They found that the rate of lung function deterioration was smaller in healthy never smokers (in both genders) than suggested previously (20 vs 30 ml/year). Another important finding was the damaging effect of smoking on the lung function decline rate which was similar in males and females. They also underlined the significance of respiratory symptoms that helped them identify a population of smokers particularly susceptible to develop obstruction. Additionally, the study

suggested that quitting smoking earlier is more protective and preventive in slowing down the progression of airflow limitation (Kohansal et al., 2009).

Severity of disease is another term used in parallel to disease progression. In COPD it is measured on the basis of FEV₁ predicted value cut off points however proposed cut-off ranges to determine severity in all recommended guidelines (ATS, 1995; BTS, 1997; GOLD, 2010; National Institute of Clinical Excellence (NICE), 2010) are not evidence-based and do not correlate with some of the outcomes. Therefore, the current trend is in favour of the use of multidimensional indices of severity such as BODE, DOSE and ADO (Celli et al., 2004; Jones et al., 2009; Puhan et al., 2009) however, these indices have some limitations and therefore have not yet been included in guidelines published (NICE, 2010). Esteban and colleagues (2009) compared them as prognostic indicators and found that BTS system of classification was slightly superior but that none of the guidelines was closely related to 5 year mortality.

Hence, FEV₁ which plays a role in all these multidimensional indices contributes to the variability in patient severity scores, depending on the cut-off points used. However the current recommendation emphasises (NICE, 2010) the use of classification criteria developed by GOLD (GOLD, 2011) which is based on deterioration in lung functions and may not completely reflect the burden of disease in these patients.

2.8 THE NEED TO MEASURE PROGRESSION

The literature review to date suggests that COPD has been the focus of research related to respiratory diseases, for many years, with studies addressing a number of different issues including: the identification of its' cause (Agusti et al., 2003 & 2010); mechanisms for the improvement of care and management (Brusasco et al., 2003; Yang et al., 2011, Qaseem et al., 2011); identification of new markers for the diagnosis of COPD (Celli et al., 2004; Cote et al., 2005; Funk et al., 2009) together with markers for the progression of the illness (Celli et al., 2004 & 2009; Puhan et al., 2009; Esteban et al., 2010) and prediction of survival (Funk et al., 2009; Puhan et al., 2009). Despite extensive research, mortality of patients with COPD has risen (Ekstrom et al., 2011).

Furthermore, the current methods of assessment of clinical outcomes in patients with COPD mainly rely on physiological measurements combined with the use of health assessment questionnaires. The review has considered commonly used outcome measures in COPD such as lung function, breathlessness, health status, exacerbations, exercise capacity, physical activity, dyspnoea, comorbidities and mortality. Based on current studies (Celli et al. 2004, Puhan et al., 2009, Jones et al., 2009), this review provides a comprehensive overview of the principle objectives, strengths and weaknesses with particular emphasis on their limitations and opportunities that should be recognized when assessing and interpreting their use (Glaab et al., 2010).

However, it is estimated that in England 842,100 of 50 million people have COPD at some point in their lives (Simpson et al., 2010) and the burden of COPD is still on the rise (WHO, 2011). Therefore urgent action needs to be taken to reduce this rising trend and also to explore and re-examine relevant physiological and psychological factors that directly or indirectly influence diagnosis, progression, treatment response and other COPD outcomes.

2.9 MECHANISMS FOR THE ASSESSMENT OF COPD PROGRESSION

2.9.1 PHYSIOLOGICAL ASSESSMENT

a. Lung Function Deterioration

FEV₁ is regarded as an important indicator of COPD progression and the most accurate clinical measure of lung function. To date, smoking cessation has been the only intervention that has been conclusively shown to alter the rate of decline in FEV₁ (Godtfredsen et al., 2008).

The original findings from TORCH (**TO**wards a **R**evolution in **Ch**ronic obstructive pulmonary disease) study (Calverley et al., 2007) demonstrated that treatment with salmeterol/fluticasone propionate resulted in a trend towards a reduction in all-cause mortality, although the mortality benefit did not reach statistical significance. In addition, the study confirmed that treatment with salmeterol/fluticasone propionate provides improvements in lung function over three years and improves COPD outcomes (Calverly et al., 2007).

Spirometry is the most commonly used test in COPD patients. It provides an overall measure of the functional status of the lung. Post-bronchodilator spirometric values are the gold standard for the diagnosis and classification of COPD. However, during screening it is not believed to be ethical to give a drug to an individual who does not exhibit any symptom of disease or may simply be at risk. Using a drug will add cost and potentially may adversely affect some subjects. Spirometry provides values for FEV₁ and FVC and obstruction is identified by a lowered FEV₁/FVC ratio (Sterk, 2004). However, there is a criticism of using FEV₁/FVC ratio based on the fact that it may over-diagnose COPD in older populations and under-diagnose it in younger (Pownall, 2010; Shirtcliffe et al., 2007; Hnizdo et al., 2006). Studies have suggested that age in years is directly associated with physiological changes that influence respiratory function in males and females (Janssens et al., 1999). Several other studies found that the cut-off point for an impaired FEV₁/FVC ratio in healthy non-smokers depends upon their age and sex (Enright et al., 1993; Hankinson et al., 1999). Therefore, the use of the fixed ratio of 0.70 as a cut-off point may lead to a misdiagnosis of COPD in the middle-aged and elderly population, irrespective of their genders. Realistically, this finding has been demonstrated in various studies (Roberts et al., 2006; Shirtcliffe et al., 2007; Hnizdo et al., 2006).

Furthermore, Schermer and colleagues (2008) found that symptoms in these patients are important, and if a patient is asymptomatic, his/her FEV₁ value becomes irrelevant. They also suggested that there are chances that an individual with an FEV₁ of less than 70 percent of predicted may always had an FEV₁ at that level. Therefore, other related factors such as symptom history, smoking history and history of occupational exposure have to be considered in order to assess and treat as patients with COPD.

Nevertheless, the Cardiovascular Health Study suggests that a FEV₁/FVC ratio of <0.70 may identify patients who are at greater risk for death and hospitalisation from COPD, even among older adults (Mannino et al., 2007). It has been shown that the FEV₁/FEV₆ ratio (FEV₆ is forced expiratory volume exhaled after full inspiration in the first 6 seconds) is as valid as FEV₁/FVC ratio (Jing et al., 2009) but does not represent an advance for globally accepted guidelines such as NICE and GOLD. The GOLD Guidelines assess disease severity on the basis of the degree of airflow obstruction, whereas the NICE Guidelines place greater emphasis on multi-dimensional assessment (Gruffydd-Jones & Loveridge, 2011).

Generally, spirometric classification has proved useful in predicting health status (Ferrer et al., 1997), utilization of health care resources (Friedman et al., 1999) development of exacerbations (Burge et al., 2000) and mortality (Anthonisen et al., 1986). Therefore, lung function is not only diagnostic for COPD but also helps in determining the disease stage, exacerbation, and can predict mortality (Schunemann et al., 2000).

The Fletcher-Peto model (1976), based on forced expiratory volume in one second (FEV_1) is the classical description of the natural history of COPD (in males). However, systemic influences, including BMI (body mass index), and subjective and objective measures of exercise tolerance have also been recognised as important for COPD prognosis (Celli et al., 2004) and were not considered in Fletcher's study.

Furthermore, the correlations between lung function and HRQL have been shown to be weak in a number of studies (Stahl et al., 2001). In contrast, the relationships have been shown to be significant in a recent trial study (Kurashima et al., 2009) but the relationship shown was greatly influenced by the treatment interventions given.

Therefore, more research is needed to further explore the issues surrounding lung function volumes including the best method of calculating reference/predicted values that are used to diagnose and classify the severity of COPD considering different physiological features such as gender, height and ethnic origin. There is also a need to examine the relationship of lung function with other COPD related outcomes in order to draw firm conclusions.

Considering the multidimensional consequences of COPD, lung function should be assessed alongside other parameters related to COPD and the present study considers lung function as a component of the proposed BOD index and as an independent variable examines its role in predicting COPD outcome.

b. Other Physiological Measurements that should be considered when Assessing COPD

The diagnosis of COPD is dependent on demonstrating limitations of airflow with spirometry and may be made if the ratio of the forced expiratory volume in the first second (FEV_1) to forced vital capacity (FVC) is below 0.70 or the lower limit of normal (LLN) (Swanney et al.,

2008). Furthermore, the degree of impairment of FEV₁ has been utilised to classify the severity of airflow obstruction in various guidelines (GOLD, ERS/ATS, NICE 2011).

Spirometric measurements are markedly affected by age (Teramoto et al., 1999). However, height and anthropometric indices are also affected by age (Perissinotto et al., 2002). Height loss may be indicative of osteoporosis and could affect the linear relationship between height and predicted forced expiratory volume in one second (FEV₁). This in turn may lead to a misdiagnosis and misclassification of COPD.

The prevalence of osteoporosis is increased in smokers. (Law et al., 1997; Cornuz et al., 1999) and osteoporosis is a known co-morbidity associated with COPD (Barnes et al., 2009; Fabbri et al., 2008 and 2010). Thus, using current height for predicting values of FEV₁ may mean that the degree of impairment of FEV₁ is subject to confounding and underestimation in an elderly population. Other measures that could be used include:

(i) Body Composition

Nutritional abnormalities are common in COPD and in smokers (Agusti, 2003; Shiozawa et al., 2010). These may present as weight loss, skeletal muscle loss and dysfunction and obesity (Franssen et al., 2008).

Body mass can be divided into two compartments: fat mass and fat free mass (FFM) (Vestbo et al., 2006). The first serves as a storage form of energy, whereas the latter contains the metabolically active organs and tissues, among which skeletal muscles are the largest part. Body composition can be determined using several methods; however, estimation with bioelectrical impedance analysis (BIA) is more convenient and can be carried out within a minute. Alterations in body composition can occur in COPD patients in the absence of clinically significant weight loss as the development of obesity can conceal loss of fat free mass and bone mineral content.

In other words, a normal balance of lean body mass and fat is associated with better health. Imbalance or higher fat content in relation to lean body mass leads to a condition that can greatly increase the risk of other life threatening conditions such as cardiovascular and other endocrinological disorders such as diabetes. BIA helps early detection of a potential

nutritional imbalance of body composition and this allows an earlier intervention and possibly prevention. BIA also provides the measurement of fluid and body mass that can be a critical assessment tool for a current health status.

Improving or maintaining BIA measurements in patients with COPD may help the body to function properly and effectively and therefore may reduce risk of illness. BIA results can help in determining and recommending specific requirements on an individual basis such as a personalised exercise plan, and a nutritional and lifestyle plan to help support good health and wellbeing.

(ii) Body Weight and Body Mass Index

Furthermore, significantly reduced body weight in advanced COPD is associated with decreased exercise performance and increased mortality. Some previous studies (Schols et al., 1993; Mador, 2002) found that the reduction in fat-free mass without a reduction in body weight was seen in 24 of 255 patients (9.4%). A reduction in body weight without a reduction in fat-free mass was seen in 23 of 255 patients (9.0%). Thus, discrepancies between measures of body weight and measures of fat-free mass are not uncommon in this patient population. Reduction in fat-free mass is a better predictor of peak exercise performance than the body mass index (Baarends et al., 1997). It is possible that decreased fat-free mass may be a predictor of poor exercise performance independent of body weight. However, the author is unaware of any studies to date that highlight this issue.

Although the effect of nutritional status on exercise performance is established (Gray et al., 1989, Hallin et al., 2010) little attention has been given to its effect on HRQL, disease progression and mortality. The present study examines the effect of nutritional status over time, change in BMI and lean body mass / fat free mass (FFM) and its relationship with other physiological measurements as a measure of the progression of the disease. This research also investigates how any change in FFM affects health status, muscle strength, co-morbid conditions, physiology and overall progression of COPD.

(iii) Inflammation and Muscle Wasting

Muscle weakness is considered to be one of the leading coexisting problems in patients with COPD. The reason that this could be responsible for patients' poor body composition is the lack of use of peripheral muscles (accessory muscles of inspiration such as intercostal muscles) among COPD patients (Decramer et al., 1997). In the present research, BMI is one of the main components of the proposed BOD index and this study provides further evidence of how this measurement could be beneficial in predicting COPD outcomes and its management

Loss of muscle mass and muscle dysfunction are now recognised as important features of COPD which contribute to poor prognosis and additional symptoms. Initial studies revealed that such limitations were due to dyspnoea (Agusti et al., 2003). In 1992, a study demonstrated that patients with COPD have limited exercise capacity owing to muscle dysfunction and skeletal muscle fatigue (Killian et al., 1992). Consequently, this observation fuelled extensive research in the field and many studies have since confirmed the role of skeletal muscle dysfunction in the pathogenesis of COPD (Gosselink et al., 1996; Demedts et al., 2006) but there is still a need for detailed research in relation to the impact of muscle weakness on health status.

COPD impairs peripheral muscle force (ATA / ERS 1999). Peripheral muscle weakness may, in turn, result in reduced exercise capacity (Gosselink et al., 1996), higher use of health care resources (Decramer et al., 1997) or decreased survival (Decramer et al., 1996, Marquis et al., 2002). Sarah Bernard (1998) suggests that muscle weakness in COPD is due to muscle atrophy and her study also suggests that prolonged inactivity and muscle deconditioning are important factors in the loss of muscle mass and muscle strength in patients with COPD (Bernard et al., 1998).

In 1998, Rantanen and co-workers launched a study that suggested that higher age reflects decreased strength. This study also reported that chronic conditions such as stroke, diabetes, arthritis, coronary heart disease and COPD are associated with weight loss. Rantanen (1998 & 2003) also found that hand grip strength is a powerful predictor of total mortality in older women. In addition, it is also documented that poor hand strength as measured by handgrip is

a predictor of disability in older people (Giampaoli et al., 1999) but the study was just confined to elderly men (age range 71-91) with different chronic illnesses such as osteoarthritis.

Therefore, the present study can be distinct in this aspect as it considers hand grip strength, dominant hand grip strength and dominant hand grip strength % predicted normal of age and sex) (Sunnerhagen et al., 2000) as a determinant of COPD outcome and the present study evaluates its influence in predicting COPD related measurements such as SMWT and outcomes such as health status and change over time.

2.9.2 SYMPTOMATIC AND FUNCTIONAL ASSESSMENT

a. Breathlessness

The predominant complaint of patients with COPD is dyspnoea during physical activity (Witek et al., 2003). Severe dyspnoea, whether acute or chronic, affects a patient's functional status and quality of life as well as other aspects of the patient's life (Moody et al., 1993).

Many studies have demonstrated various clinical techniques for rating dyspnoea including the modified Medical Research Council (MRC) scale (Bestall et al., 1999, Calverly et al., 2003; Pitta et al., 2005). All are significantly correlated and virtually identical in evaluating dyspnoea in patients with COPD.

Dyspnoea (shortness of breath) is a complex subjective sensation of functional disability in patients with different forms of cardio-respiratory diseases (Stenton, 2008). There are various tools available for assessing dyspnoea. For example, the measurement of dyspnoea with activities of daily living using clinical dyspnoea ratings such as the Medical Research Council (MRC), the Mahler's Dyspnoea Index (MDI) which is composed to two parts Baseline Dyspnoea index (BDI) and Transitional Dyspnoea Index (TDI) (Mahler et al., 1988), the Oxygen Cost Diagram (OCD) (Chhabra et al., 2009) and the measurement of dyspnoea during exercise using the Borg scale, which is a RPE (Rate of Perceived Exertion) scale to rate degree of breathlessness, uncomfortableness and fatigue level after an exertional activity such as a walk test (Burdon et al., 1982).

Every tool has its own advantages and disadvantages. For example, MDI is a complex and a very time consuming questionnaire both for researchers and for patients but at the same time it has proved more sensitive for assessing short term changes in the degree of breathlessness in patients with COPD (Ansari et al., 2009; Chhabra et al., 2009). Studies also suggest that the BORG scale is relatively costly and needs instruments, time and space. It cannot be applied to every subject as not all patients with COPD can perform the exercise test.

In the 1950s, Fletcher and co-workers invented a tool to evaluate the degree of functional disability in subjects who have shortness of breath. The full version of the questionnaire with its scaling system was published in 1959 (Fletcher et al., 1959). Several versions are available. The version utilized in the present study is the five point scale demonstrated in table 3.2 (chapter 3) (Scale from 1-5). However, the modified version of MRC (MMRC, Scale from 0 to 4) is virtually identical and appears to be more logical as absent breathlessness is scored zero. The MRC scale is one of the most validated and widely used instruments to assess the degree of impairment due to shortness of breath in COPD (Bestall et al., 1999), bronchiectasis (Koulouris et al., 2003) and idiopathic pulmonary fibrosis (IPF) (Papiris et al., 2005). It has also been used in other systemic illnesses that cause breathlessness such as sickle cell disease. (Declaux et al., 2005). Patients with COPD predominantly complain of dyspnoea during physical activity. The severity of dyspnoea and its correlation with various pulmonary physiological tests in COPD have been published (Mahler et al., 1988; Eltayara, 1996; Bestall et al., 1999). Studies have also demonstrated that the MRC scores are significantly correlated with walking distance and mortality (Celli et al., 2004; Nishimura et al., 2002).

As the MRC is sensitive when assessing long term changes in the degree of dyspnoea (Bestall et al., 1999, Calverly et al., 2003; Pitta et al., 2005; Ansari et al., 2007), this is the assessment of choice when measuring functional impairment in patients with COPD due to shortness of breath.

The MRC scale is recommended as complimentary to spirometric measurements (FEV_1) in describing functional disability in COPD patients and is used worldwide (Stenton, 2008).

The MRC scale is an easy to fill questionnaire that requires only a few seconds. It can be self-administered by asking the subject to choose the statement (out of 5) that best describes their clinical condition. It can be administered by an interviewer with all the options of the MRC

scale framed in the form of questions/statements. No additional resources such as space, equipment or any training is required to fill in this questionnaire. Additionally, there is no copyright issue involved and it is readily available to use for clinical and research purposes.

The only disadvantage of the MRC scale is its relative insensitivity to acute and sub-acute changes of disease status. For example, change in disease status can be demonstrated after lung volume reduction surgery (LVRS); however, it is unlikely that all patients who undergo LVRS will demonstrate any significant improvement or deterioration in their entire MRC grades. The insensitivity may be due to a certain ambiguity in the MRC grading system, such that any subjects who can leave the house but can only walk 100 yards or less does not clearly fall into either Grade 4 or Grade 5. Breathlessness during dressing and undressing is an additional indicator of severity.

In the present research, dyspnoea is one of the vital components of the proposed BOD index and this research evaluates its significance in predicting COPD outcome and its change over time with respect to disease progression.

b. Exercise Test

Patients with COPD often become severely inactive in their activities of daily living (ADL) such as housework, cooking, eating, bathing, dressing, grooming, and leisure (Katz et al., 1983). This inactivity leads to deconditioning and muscle weakness because of disuse. Several laboratory tests are available for the objective evaluation of functional exercise capacity, such as cardiopulmonary exercise testing, the Shuttle Walk Test and the 6-minutes walking test. Cardiopulmonary exercise testing is considered the gold-standard in the evaluation of patients with pulmonary diseases as it is monitoring, breath by breath, several cardiopulmonary variables, including maximal oxygen uptake, pulmonary output of CO₂, minute ventilation, and cardiac frequency. However, cardiopulmonary exercise testing requires dedicated laboratory equipment and expertise and it is difficult to perform in general clinical settings (Papaioannou et al., 2009).

Pulmonary rehabilitation proved to be an effective intervention for the management of COPD (George & Monica, 2011; ZuWallack, 2007) and the six-minute walk test (6MWT) is widely used as an outcome measure in pulmonary rehabilitation programs (Jenkins et al., 2010).

Studies suggest several factors influencing the 6MWT in patients with and without COPD. There are various co-founders that can alter test results particularly in elderly individuals. These factors include age, body weight, mental health, and comorbidities (Enright et al., 2003). Poor nutritional state (Palange et al., 1995 and 2003) and breathlessness are manifestations of COPD that can also reduce 6MWT (Marin et al., 2001; Oga et al., 2002). Muscle strength in the lower limbs has previously been shown to be an important factor in determining the 6MWT (Gosselink et al., 1996).

Despite the number of confounding subjective and objective measurements, this test has gained importance globally and has been found to be reliable, safe and easy to apply. The 6-minute walking distance (6MWD) has been shown to be an independent predictor of mortality in COPD patients, as shorter walked distance was confirmed to be associated with a higher mortality. (Cote et al., 2007, Enright et al., 2010). Another report (Calverly 2007) has shown that the 6MWD declines over time and that this decline is most important in patients with severe airflow limitation (i.e. $FEV_1 < 50\%$ predicted). Interestingly, in patients with severe COPD the decrease in FEV_1 over time has been shown to be relatively small, suggesting that decline in exercise capacity occurs independently of changes in lung function. Studies also suggest that the six minute walk test is a good predictor of mortality in patients with interstitial lung disease (Eaton et al., 2005), pulmonary hypertension (Miyamoto et al., 2000), and acute respiratory distress syndrome (ARDS) (Herridge et al., 2003). On the basis of above discussion, it is evident that this test plays a significant role in detecting changes and improvement which cannot be detectable in spirometry results especially in severe and very severe COPD.

The exercise test has some disadvantages that may limit its application to all disease population and its use in all clinical settings (ATS 2003; Reybrouck 2003). In terms of its application to COPD patients, not all patients can perform a meaningful walk test. Also, considering the fact that COPD patients are generally over 60 years of age, it is likely that patients may have any associated comorbid condition that may confound the result or influence patients' performance in carrying out this test (Enright et al. 2003). For example, it will not be comfortable for a patient with osteoarthritis or osteoporosis to carry out this test.

Additionally, for patients with severe COPD; a six minute walk test may be relatively unsafe as these patients have a severe form of impaired gas exchange, such patients when challenged with an increase in demand (as in six minute walk test), have a higher risk of oxygen

desaturation (Hadeli et al, 2001). Another study suggested that patients with severe COPD are at higher risk of developing arterial hypoxemia during exercise and during daily routine activities (Garrod et al, 2000). Therefore, close monitoring of oxygen saturation and arterial blood gases may be needed during the exercise test. Another study observed oxygen desaturation in 90% of the study participants during a six minute walk test (Ozalevli et al, 2007).

The exercise test is time consuming and therefore not performed in primary care where the components of BOD are routinely recorded (Puhan et al., 2009).

c. Duration of symptoms

A symptom is a subjective representation of a disease. There are two types of symptoms. Sudden onset and short duration is termed “acute” whereas gradual onset and long standing is termed “chronic”. Acute symptoms commonly occur in cases such as cholecystitis, appendicitis or acute gout that require immediate therapeutic or surgical treatment. On the other hand, chronic symptoms are common in conditions such as rheumatoid arthritis, osteoarthritis and chronic obstructive pulmonary disease that require long term treatment, regular monitoring and follow up with other secondary interventions to minimize disease progression and to control patients’ symptoms and their negative impacts on patients’ life. In very severe cases, surgical intervention may be applied.

As the symptoms in patients with COPD are usually not very prominent, a typical pathway for COPD patients is that it is initiated generally after 10 years of cigarette smoking when symptoms appear that catch the patient’s attention leading to them seeking a physician’s advice. Patients with COPD generally develop a symptom of chronic cough accompanied by a small amount of sputum. It is also very unusual that patients, with COPD, complain of shortness of breath, during exertion, below the age of 40, after that age breathlessness becomes more common and may well be recognised by the age of 50 years.

To date COPD is often undiagnosed or misdiagnosed (Black, 2009) until it is advanced. Earlier diagnosis could markedly reduce systemic manifestation, comorbidity, disability and improve health status (Jones, 2006). Key areas for improvement include enhanced case identification, improved quality and interpretation of findings on spirometry, and increased use

of tools such as differential diagnosis questionnaires and in order to achieve optimal outcomes, there is a need to explore every aspect of the disease to establish a firm diagnosis, which will lead to the development of methods for monitoring progression more effectively in these patients.

The literature review reports that “symptoms” of patients with COPD and their relationship with other COPD outcomes have not been studied as yet. Thus the present study examines the duration of symptoms in patients in relation to COPD outcomes.

2.9.3 HEALTH ASSESMENT

Globally, the conditions with a target impact on health status are arthritis, COPD and heart failure (Alonso et al., 2004) Therefore, there is a need to understand the relative contribution of respiratory impairment, physical disability, comorbidities, coping, age and physiological and psychological variables on understanding health status in patients with COPD.

a. Health Related Quality of Life

The term “Quality of life” is defined as the gap between desired and achievable personal and social activities (Jones et al., 1991). Quality of life may be difficult to measure accurately. Patients with COPD experience a reduction in HRQL, which includes reduced ability to work and to participate in physical and social activities (Stahl et al., 2003). This concept is encapsulated by the term "health-related quality of life" (HRQL).

There are two types of questionnaires available for assessment of health related quality of life in patients with respiratory illness. “Generic questionnaires” are used to perform comparative assessments between populations of patients. However, some of these types of questionnaires such as the Sickness Impact Profile or Short Form 36 may be rather insensitive to changes in health or vary over time (Jones et al., 1997). The other available types of questionnaires are “the disease-specific Questionnaires” that mainly include Chronic Respiratory Questionnaire (CRQ) (Guyatt et al., 1987) and St. George’s Respiratory Questionnaire (SGRQ) (Jones et al., 1992). The CRQ attempts to overcome some of the potential difficulties when using generic questionnaires. In CRQ the questionnaires are customized to the individual patient so that they

can compare their current state of health with their previous ones. The SGRQ is however the most widely used questionnaire to assess health status in these patients and has the advantage of allowing direct comparison between different patient populations and treatment groups and has been shown to be responsive when used for these comparisons (Jones et al., 1991, Jones et al., 1994). Because of their subdivision into different components i.e. symptoms, activity and impact; in-depth analysis of the health status impairment are possible in these patients. The SGRQ is also effective in assessing changes over time in health status and a 4-unit change in the scores considered as clinically significant (Jones, 2002). Some recent studies have supported the use of SGRQ in patients with COPD by showing its relationships with other systemic biochemical parameters (Broekhuizen 2006, Garrod et al., 2007, Seemungal et al., 2007).

The present study looked at health status in two ways. Firstly its relationship with other COPD markers, including multidimensional indices and secondly, its change over time in patients with COPD. The present study also attempted to enhance this assessment by introducing psychologically influenced wellness status in these patients.

2.9.4 HEAMATOLOGICAL ASSESSMENT

It has been suggested that anaemia could be a significant factor that influences prognosis in COPD patients as decreased haematocrit and haemoglobin levels in these patients are associated with frequent hospitalization and therefore increased mortality (Chambellan et al., 2005).

a. C Reactive Protein (CRP)

C Reactive Protein (CRP) is an acute phase plasma protein elevated particularly during exacerbations of COPD patients (Hurst et al., 2006, Wilkinson et al., 2006). A high concentration of CRP 2 weeks after an exacerbation predicts the likelihood of recurrent exacerbation (Perera et al., 2007).

However, plasma concentrations of CRP in stable COPD patients are related to mortality in patients with mild to moderate disease (Dahl et al., 2007), but no association are found in

severe and very severe patients (de Torres et al., 2008). Elevated levels of CRP are also associated with a worsening of COPD outcomes, such as impaired health status and exercise capacity. Another study suggests CRP as a significant predictor of body mass index (BMI) (Broekhuizen et al., 2006). There is a controversy about the relationship of CRP with FEV₁. In cross-sectional studies CRP is related to FEV₁ whereas no association was found in longitudinal studies (Fogarty et al., 2007) with the progressive decline of FEV₁.

This study investigates the role of CRP concentration as a marker of prognosis in COPD patients and to examine the possible correlation between CRP concentration and other COPD markers of progression.

2.9.5 PSYCHOLOGICAL ASSESSMENT

Our understanding about identification, diagnosis and management of the clinical signs and symptoms of COPD has considerably improved during the last decade but its psychosocial burden is often underestimated, unrecognised and may be neglected (Kelly & Lynes, 2008; Bauldoff, 2009).

COPD generally involves progressive deterioration in pulmonary function which results in increased shortness of breath and reduced ability to perform activities of daily living (ADLs). It also involves variation and alterations in the social roles of patients, their relationships and self-perception and so necessitates continual psychological assessments and adjustment. (Kelly and Lynes, 2008). Thus the prevalence of conditions like anxiety, depression and mental impairment may be increased in COPD patients and ultimately may impair their illness severity, prognosis and natural wellness.

Considering the slow progression of COPD, and the need for patients to maintain a good quality of life, it is imperative that any psychological issues are not only recognised but also managed effectively. These psychological issues need to be explored however no assessment tool is available for the evaluation of the factors that precipitate mental stress and other psychological problems in these patients. Some of the major psychological issues common in patients with COPD are discussed below:

a. Anxiety and Depression

Depression is a psychological disorder that is characterised by mood variation, physical function and social interactions whereas anxiety is defined as a feeling of apprehension and fear characterized by physical symptoms such as palpitations, sweating, and feelings of stress. Both terms are commonly used together as patients with depression usually have some degree of anxiety and vice versa. The incidence of anxiety and depression is more common in COPD patients than in patients with other long standing impairments as well as in the general public with no obvious disease (Putman-Casdorph & Mc Crone, 2009). However, little attention has been given to psychiatric comorbidities in these patients. Compromised breathing may be the key cause of depression. Other known causes that are linked with anxiety and depression in COPD patients are increased mortality, decreased functional status and impaired HRQL. However, there may be some other risk factors that cause anxiety and depression in these patients that have not yet been studied. These risk factors may include socioeconomic status, illness perception, wellness level, smoking status, passive smokers, body mass index, lean body mass, and muscle strength together with occupational history and medication. Mental and psychological factors are components that describe the level of wellness. The present study investigates the possible correlation between level of wellness and COPD outcome. By focussing on wellness related issues in treating COPD, patients can minimize the frequency of exacerbation. There may also be improvements in the outcome of acute exacerbations. Recently a study (Funk et al., 2009) showed that BODE index is higher-up than GOLD (Global Initiative for Obstructive Lung Disease) to explain anxiety and depression in patients with COPD.

Thus, overall the role of psychological health is an important factor in achieving a balanced attitude to the effects of their illness for the patients in order to maximize their wellness and the present study aimed to explore psychological status of these patients that may be helpful to control disease progression in COPD.

b. Role of Wellness in and its Use as a Measure of COPD Progression / Outcome

As opposed to illness perception and health status, there is another term used to describe patient's health which is "Wellness". Travis (1978) has highlighted the variety of

psychological functions that can influence health status. He viewed the current apparent state of existing life as being merely the tip of an iceberg with multiple levels of complexity below the surface (Figure 2.7).



Figure.2.7. Wellness Concept by John W Travis, 1978, 1998, 2004

To understand all the factors that are responsible for supporting current health status, it is therefore suggested to look beyond the tip of the iceberg to consider that which is normally invisible and/or un-focussed as explained in the figure above. The first level beneath current state of health (HRQL) is the lifestyle/behavioural level, followed by psychological, mental stress and motivational level and the deepest of all is the spiritual/being. A combination of all these levels tends to indicate our overall state of wellness (Travis, 1970).

A definition of wellness as “the degree of positivism and enthusiasm about healthy life” mainly comes from the capacity of an individual to manage feelings and related behaviours including the realistic assessment and realisation of one’s limitations, development of autonomy and the ability to cope effectively with stress (Manderscheid, 2006). This coincides with the concept behind the development of a wellness questionnaire for this study.

No specific study, in health research, has explored and analysed the role of wellness status in disease prevention, disease progression and disease monitoring (Schwartz and Holtorf, 2008).

Wellness is a life style a person adopts to acquire the highest level of wellbeing. It is a process that is responsible for developing awareness, energy and knowledge in people to realize that there is no end-point before death, therefore, always to try to resist with confidence whenever something goes wrong in your life, for example, in the event of any chronic illness. Wellness is an integration of a body, soul and mind. It is a kind of healthy belief (Travis, 1970). It enables a person to realize that everything we observe, think, perform and feel has a great impact on our state of health and state of wellbeing. Therefore, our activities of daily life including personal, social and spiritual aspects produce a serious impact on illness progression and recovery in both positive and negative ways.

COPD follows a typical un-wellness trajectory of long-term restrictions and limitations with sporadic and relatively serious episodes (Murray et al., 1997) called exacerbations. Sometimes the exacerbation attacks are very severe resulting in death. However, many patients survive many such episodes. Studies have suggested that many of these patients experience a lower health status than patients without exacerbations. Major problems arise from dyspnoea that, in turn, lead to immobility, dependency on others (family, friends, relatives, neighbours, health care workers) and lack of energy to perform daily tasks such as bathing, gardening, jogging and recreational activities. It could result in the social isolation of a patient (Skilbeck et al., 1998; Ek et al., 2008). Therefore, it could be expected that patients with such impairments have numerous preferences, wishes, needs, expectations and requirements and all these factors may help to ameliorate their overall condition and contribute to an improvement in their degree of wellness. Previous studies have suggested that patients with severe COPD believe that their limitations are irreparable and that the consequences are due to an irreversible damage of the airways that cannot be improved or repaired and therefore they do not actively express a wish for help. These findings suggest that care at this stage of the disease should focus on improving daily lifestyle instead of simply aiming to improve the functioning of the lungs (Habraken et al., 2008). Additionally, another study (Monninkhof et al., 2004) consisting of qualitative interviews suggest that the SGRQ and possibly other existing HRQL instruments might fail to capture the full experience of patients in self-management studies. The need for

more elaborate qualitative research on this subject is indicated and present research will be an attempt to fill this gap.

2.9.6 MULTIDIMENSIONAL MODELS FOR ASSESSING PROGRESSION

a. Multidimensional Assessment of COPD – BODE, DOSE ADO, and BOD

FEV₁ is the key measure used for diagnosing, classifying and managing COPD. Classically, FEV₁ and age are the two vital prognostic indicators identified in patients with COPD (Fletcher et al., 1976, Traver et al., 1979; Anthonisen et al., 1986). However over the last ten years COPD has been regarded as a multicomponent disease and thus factors such as dyspnoea (Nishimura et al., 2002), malnutrition (Landbo et al., 1999), hospitalization related to COPD exacerbations (Soler-Cataluna et al., 2005), exercise capacity (Oga et al., 2003), physical activity (Garcia-Aymerich et al., 2006), pulmonary hypertension (Ostwald-Mammosser et al., 2006), inspiratory capacity (8), lung density measurements by computed tomography (Casanova et al., 2005), muscle mass (Marquis et al., 2002), HRQL (Domingo-Salvany et al., 2002), and other markers (Cote and Celli, 2007), have also proved to be individual, effective prognostic indicators. Therefore, employing several variables in the measurement of COPD improves its assessment, and incorporating these variables into a multidimensional model improves their prognostic power as compared to traditional measures based exclusively on FEV₁. Adopting this approach, Celli and colleagues (2004) proposed a model to measure severity and prognosis of the disease; the model BODE (BODE – BMI, airflow Obstruction, subjective Dyspnoea and Exercise test), uses a 10 point scale. According to Celli and co-workers (2004), “The BODE index, a simple multidimensional grading system, is better than FEV₁ at predicting the risk of death from any cause and from respiratory causes among patients with COPD”. This index illustrated that this multi-dimensional assessment is a better predictor of the risk of death both from all causes and from respiratory causes than FEV₁ alone (Figure 2.8). The figure shows that patients with a higher quartile in the BODE index have the least probability of surviving for 4 years or more, this contrasts to those with a lower BODE quartile.

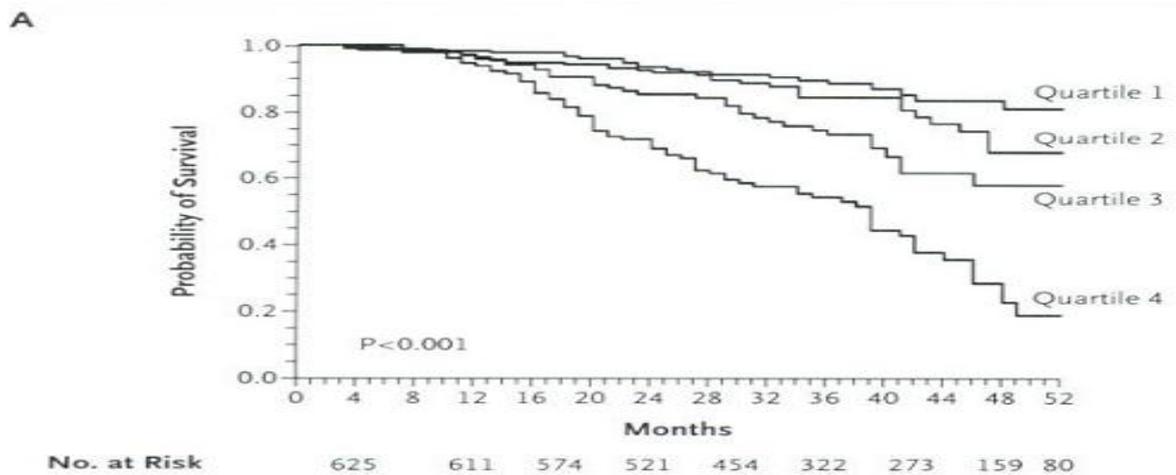


Figure 2.8. The worst quartile BODE index showed a mortality of 80% in four years in a hospital cohort (Celli et al., 2004)

The efficiency of the BODE index has been assessed in various studies (Ong et al., 2005; Imfeld et al. 2007; Lederer et al., 2007; Pampeo and Mineo 2007; Martinez et al., 2008; Cote et al., 2008; Holland et al., 2010; Ko et al., 2011) which support its value with respect to COPD outcomes including health status, anxiety and depression, hospitalization and mortality. However, COPD patients are mainly managed in GP surgeries and the BODE index is rarely used in these settings because exercise capacity (also known as the six minute walk test (SMWT), which is one component of the BODE index, cannot be easily performed and measured (Puhan et al., 2009). In addition, the six minute walk test has various sources of variability which makes this test controversial. The sources of variability in SMWT include: patient’s motivation, height, weight, gender, age, comorbid condition of a person and day to day variability (ATS Statement, 2002). Studies have also demonstrated that the SMWT is reduced significantly in patients with severe or very severe disease (GOLD stages 3 or 4) (Pitta et al., 2006; Watz et al., 2009). BODE investigators have mainly recruited hospital patients with severe and very severe stages (70% of the cohort had FEV₁%predicted of 50 or less). The index was optimized to predict 12 months mortality and it is believed that the factors affecting short term survival may be different from those influencing longer term survival. The gender based variation has not been explored in BODE studies. In addition, Puhan and colleagues (2009) found that BODE underestimated the risk of mortality in younger patients and overestimated in patients with mild symptoms, in their cohort. They used this study to derive another multidimensional index “ADO”. The ADO index is composed of Age, Dyspnoea Score

and Airway obstruction and is another major development in assessing COPD progression (Puhan et al. 2009). The ADO index, a new score for predicting a patient's risk of dying of COPD appears to give better results than the currently used BODE index (Puhan et al., 2009). However only one study (Chen et al., 2011) has assessed the ADO index and validated its prognostic importance in patients with COPD. The ADO index used Swiss and Spanish cohorts and looked at 3 year mortality risk in these patients. By introducing age, the ADO index has been criticised because age is the most important determinant of survival, independent of disease status and diagnosis. Age has limited value in the stratification of a specific disease process (Celli et al., 2009).

An alternative outcome to mortality is hospitalization and Jones and colleagues (2009) developed the DOSE index that contains a combination of subjective and objective measurements i.e. dyspnoea (D), airway obstruction (O), smoking status (S), and frequency of exacerbation (E). The index proved to be a simple tool to assess disease severity. However, this index was mainly aimed at examining its relationship with health status, future events such as hospitalisation and respiratory failure and also management and did not take account of mortality which is one of the main COPD outcomes of interest both for patients as well as for their health care providers. Although a recent publication in the European Respiratory Society (ERS, 2011) found DOSE as a valuable predictor of mortality no further researches have been carried out to support and/or to validate their findings. In addition “S” in the DOSE index represents current smoking status, a clear risk factor for frequent exacerbations and not past smoking history (pack years) which relates to comorbidities (Eberly et al., 2003) and therefore mortality.

The discussion above suggests that no index fully reflects the burden of disease and there is still a need to develop an index that can be easily applied to a wider population without limitations (NICE, 2010). NICE guidelines have also suggested that a multidimensional assessment tool should be evaluated with Caucasian populations and explore COPD related outcomes other than mortality. The present study takes account of NICE recommendations by introducing a new index “BOD”. BOD is an alternative to BODE which is more easily applicable in primary care. The requirements for the SMWT may not be available in general practice or suitable for all patients. Additional resources such as time, trained staff, and space are also needed. Furthermore the mobility of the patients can also influence the performance

during SMWT (NICE, 2010). Additionally, the present study consists of Caucasian males and females and explores their relationship with mortality, probability of longer survival and health status. In other words, this study applies the BOD index to a cohort of primary care patients with COPD and will be discussed further in chapter 4.

2.10 Confounding factors in the Assessment of COPD.

COPD is one of the leading causes of morbidity and mortality in industrialized and developing countries. The mortality rate for COPD is rising and COPD will most likely become the third leading cause of death worldwide by the year 2020 (Siafakas et al., 1995; Murray et al., 2000, WHO Report, 2008).

Forced expiratory volume in one second (FEV_1) cut-off points established the severity of COPD. Various guidelines have been published to classify the severity of disease that includes ATS (1995), BTS (1997), GOLD (2001) and consensus guidelines from the ATS-European Respiratory Society (ATS-ERS) in 2004 and Esteban and colleagues (2009) compared them as prognostic indicators. Although the BTS system was slightly superior, none of the guidelines was closely related to 5 year mortality. The recent study shows harmonisation of the NICE severity grading with GOLD (Gruffydd-Jones and Loveridge 2011) that could potentially increase very considerably the number of patients diagnosed with the disease. However, there is little evidence that asymptomatic patients fulfilling the GOLD Stage 1 criteria have an increased risk of deterioration in health status or FEV_1 . Therefore, GOLD classification does not fully reflect the severity of the disease and therefore the recognition that assessment of COPD disease severity requires a multi-dimensional approach has led to the development of multi-dimensional indices.

Therefore there was a need for a comprehensive staging system that allows for more adequate categorization of patients with COPD and the development of the BODE Index (Celli et al., 2004) was the milestones in this regard. However there are a number of limitations with BODE that are discussed in the next section.

2.10.1 Comorbidities

COPD patients are associated with significant comorbid diseases with one study reporting that 84% of COPD patients have at least one or more co-morbidities (Barnes and Celli, 2009) compared to comorbidities in control subjects which was reported 63% (Van Manen et al., 2001). Studies suggested that Co-morbidity plays a major role in health status (Ferrer et al., 1997; Van Manen et al., 2001) and health services utilisation independent of lung function measured by FEV₁ (Oostenbrink et al., 2004).

The most common comorbidities in COPD include osteoporosis, arthritis, cardiovascular diseases and cancer (Sin et al., 2006) in which cancer and cardiovascular disease are major the comorbid conditions related to high mortality (Wasswa-Kintu et al., 2005; Sin et al., 2005). The high prevalence of comorbid conditions may be related to malnutrition (Sin et al., 2006), inactivity, smoking, steroid treatment (Iqbal et al, 1999), systemic inflammation (John et al., 2005), elderly patients, and patients with low BMI and FFMI (Gosker et al., 2002; Vestbo et al., 2006; Bolton et al., 2004). However it is still not clearly understood whether comorbid conditions in COPD is the cause or an effect of COPD systemic consequences (Sin et al., 2006). Clearly more work is required to explore this and the potential link between COPD, mortality and comorbid conditions (Sin et al., 2006).

To assess morbidity in COPD or any other disease, a complete medical history and full physical examination is needed to look for signs of any other chronic illness and record the finding on a Charlson Comorbidity Index which quantified the effect of comorbidities (Quan et al., 2011). The overall comorbidity score reflects the cumulative increased likelihood of one-year mortality; the higher the score, the more severe the burden of comorbidity.

2.10.2 Exacerbations

Exacerbations are characterised by acute patho-physiological deterioration reflected by worsening of COPD symptoms. Patients with COPD are prone to exacerbations that are an important determinant of health status, morbidity and mortality (Wedzicha, 2002). Therefore, it becomes an important outcome measure in the study of therapy in COPD and a few studies have addressed the effect of exacerbations on disease progression, severity and health status in COPD patients (Seemungal et al., 1998; Aaron et al., 2002; Miravittles et al., 2004).

Predicting which patients may be more susceptible to exacerbation is not a simple function of the degree of impairment of FEV₁ (Ansari et al., 2007). Interestingly, Martin and colleagues (2008) found that a multidimensional score (BODE) is a better predictor. But Soler-Cataluna (2009) and co-workers concluded that severe exacerbation and BODE index are two independent risk factors for death in male COPD patients.

2.11 Conclusions

The literature review has shown that there is no drug therapy that significantly alters the progressive worsening of lung function (Michele et al., 2010). Literature review also suggests that the main problems with COPD are twofold. First, its multidimensional consequences and secondly its development and progression that dramatically vary between individuals (Mannino et al., 2006) suggesting more research is necessary, focussing on an in-depth evaluation of measures to determine the progression of the disease.

COPD is a chronic illness that has an impact on health status. How well a patient actually feels and responds (in the presence of disease symptoms, lung function deterioration, and comorbidities) determines the progression and consequences of the disease on their health.

To date smoking cessation and smoking bans in public places (particularly in developing countries) is the only intervention that has a substantial positive effect not only on disease progression but also on other COPD outcomes (Anthonisen et al., 1994; Papadopoulos et al., 2011). However the burden of COPD is still on rise worldwide (WHO, 2011) and therefore there is a need to do more in this respect to reduce the COPD burden not only for its sufferers but also for health care providers. Identification of the rate of progression of the disease could be used to improve outcomes, reduce health care utilization and cost.

Therefore, this thesis has tried to identify those factors and/or markers in these patients. The ability to fight the disease may thus be dependent upon the sense of self responsibility, physical, emotional and mental wellbeing, potential stress related factors that make disease worse and these all comes under the umbrella of a term “wellness” and the present study explore this aspect of disease.

Chapter 3

METHODOLOGY

The methods adopted in this study comprise:

A. Quantitative Analysis

- Evaluation of BOD and Other Markers of COPD Progression
- Evaluation of Physical parameters that may relate to COPD.

B. Qualitative Analysis

- Evaluation of Wellness (Psychological Marker of COPD).

A. Quantitative Analysis

3.1 Study Background

The present research is a continuation of a pilot study carried out in 1999-2002 when a database of 634 suspected COPD patients was assembled. The measure used for the determination of COPD was spirometry. This was carried out in general practice surgeries in Sunderland using British Thoracic Society Criteria (BTS, 1997). 458 subjects were deemed to satisfy the requirements for a diagnosis of COPD. At that time, the measurements were carried out by a Respiratory Research Team at the Chest Clinic at Sunderland Royal Hospital led by Dr. Niall Keaney. In the present study, it was decided to follow the surviving members of the original cohort. Analysis for the study undertaken here was carried out in 2007-2008 and again a year later in 2008-2009 to examine the progression of the disease and its outcomes.

Hence the data presented for time 1 (1999-2002) was collected by Andrea Kay and the data presented for times 2 and 3 was collected by the author of this study.

The detailed methodology of the present study including design, measurements and study tools is explained below.

3.2 Study Design

This is a longitudinal, retrospective and prospective / observational study.

Following the publication of the British Thoracic Society's COPD guideline in 1997, spirometers were introduced in GP clinics and spirometry training was provided into the local primary care network. The database was initially established for lung cancer screening under the supervision of Dr. Niall Keaney, Consultant Chest Physician by identifying patients who were at risk of developing lung cancer including smokers, those with a history of dust exposure, breathing related symptoms, spirometric evidence of lung function impairment). The patients were recruited from Asthma Clinics in primary care and information was collected by Andrea Kay (Respiratory Physiologist and Research Assistant to Dr. Keaney). The following information was recorded during the establishment of the initial database:

- Name (date of birth, NHS number)
- Demographics (smoking status and pack years, age, gender, height, weight, BMI).
- MRC Dyspnoea Score
- Spirometry (FEV₁, FVC, FEV₁% predicted, FEV₁/FVC ratio)
- Respiratory Symptoms (cough, sputum, chest pain, breathless, wheezing)
- Occupational history (exposure to dust/other pollutants)
- Comorbid conditions.

In the initial database there were 634 patients either with suspected COPD or at risk of developing the disease. In 2007-8, the data base was reviewed by the researcher (Khalid Ansari) and those patients who met the spirometric evidence for COPD, as per the standard guidelines (BTS, 1997; GOLD, 2004) were invited to a follow up visit (n=458). All participants were contacted *via* letter containing an invitation request, information sheet about the study, consent form and a slip asking if they were willing to participate and if so asking for their availability so that recruitment session could be scheduled. The invitation letters were

sent a second time to those who did not respond to the initial letter. A telephone contact were also made to those whose contact numbers were available on the hospital databases. Therefore, all possible efforts, within ethical limits, were made to recruit as many participants as possible for this study.

The ethical approval for the data collected between 1999 and 2002 was obtained in 1998.

Ethical approval was also obtained from Sunderland Local Research Ethics Committee (LREC) and the University of Sunderland Ethical Committee. Approval to carry out the research was granted by City Hospitals Sunderland Foundation Trust and Sunderland Teaching Primary Care Trust (TPCT) in July, 2007.

Subsequently, ethical approval for the amendment made in relation to the assessment of wellness in the COPD cohort was obtained in March 2009.

To relate the multidimensional indices with mortality, the participants who died between 1999 and 2010 were identified. The names and NHS number of the subjects in the original 1999-2002 cohort were submitted to the PCT and from the Registrar General's data those subjects that were deceased were obtained, together with their respective date and cause of death. The follow up therefore for mortality was complete (100%).

3.3 Study Population

At the commencement of this study there were 458 patients of the 634 originally recruited in 1999-2002, all of whom had a clear diagnosis of COPD. This was based on the following exclusion criteria (BTS 1997):

1. Patients <40 years of age, as COPD below 40 is very unlikely.
2. Patients who refused or did not have the ability to give informed consent as according to current ethical guidelines, it is one of the essential requirement.
3. Patients with any terminal illness were not contacted, as performing spirometry and an exercise test is not safe in individuals with terminal illness.

4. Patients who were on a pulmonary rehabilitation programme during the study, as it is an avoidable confounding factor with respect to COPD outcomes.
5. Patients with >3 exacerbations in the past 12 months as such patients have a high mortality risk.

Patients from the original cohort were invited to attend the Chest Clinic, Sunderland Royal Hospital on two occasions; first in July 2007/2008 and then for follow up in 2008/2009. There were thus three sets of data at the end of the collection phase, i.e.

1. Data from 1999-2002 – collected by Andrea Kay (Experienced Research Physiologist at Chest Clinic in Sunderland Royal Hospital).
2. Data from 2007-2008 – collected by researcher or Andrea Kay.
3. Data from 2008-2009 – collected by researcher or Andrea Kay.

Subjects were contacted by letter with a patient information sheet about the study and their participation. Once they had agreed in principle by returning their signed paper slip stating that they were willing to be contacted for the study, they were then contacted by telephone by either the researcher himself or Andrea Kay so that any queries could be raised regarding recruitment and/or arranging taxis between their homes and the hospital, and also to discuss any research related issues. At the clinic appointment patients were given the opportunity to discuss the study further and then asked to sign a consent form. They could refuse to take part at this point and future disease management would not be affected.

3.4 Physical Measurements Undertaken.

The following measurements and assessments were carried out on eligible patients at the chest clinic. Patients were recruited one by one by the researcher using the same equipment for all participants.

The following measurements and assessments were carried out in eligible patients.

- a. Patient report form including name, date of birth, date of visit and other demographical details (mentioned below).
- b. Height
- c. Armspan
- d. Weight
- e. Body Mass Index
- f. Smoking History
- g. Historic occupation details to determine subjective pollution exposures.
- h. Current Medication
- i. Lung Function Measurements
- j. Fat Free Mass
- k. Six Minute walk distance (SMWT)
- l. Hand grip strength measured using a hand dynamometer.
- m. Clinical Examination
- n. Blood Samples
- o. Respiratory questionnaire (SGRQ).
- p. Charlson Index to evaluate comorbidities (table 3.4).
- q. Subjective disability using the MRC dyspnoea score.
- r. Wellness assessment questionnaire. (Sunderland Wellness Respiratory Questionnaire)

Each patient's participation took an average of 1-1.5 hour per session.

All of the measurements were carried out by the researcher or by the other research team member, who is a qualified, trained and experienced clinical physiologist. However, the main researcher/author was present at all times during the patient measurement sessions.

3.5 Study Instruments and Measurements

a. Patient Report Form

This form was completed by each participant and detailed information was recorded about the study subjects' demographics and other relevant information including patient identification number, name, date of birth, active and passive smoking history, height, arm span, weight, BMI, symptoms at present, symptom duration, current medication, history of exacerbation, history of medication, and physical examination findings.

b. Height

Height was recorded using a stadiometer without shoes (with socks or stocking), heels together, freely hanging arms, and head in Frankfurt plane (an anatomical reference point of the human skull in which the superior border of an external auditory meatus is on a horizontal plane with the inferior border of the eye orbit). The inclusion criteria for this part of the study included the inability of the patient to stand erect without support and the ability to extend both arms comfortably, without any spinal, vertebral deformity or other connective tissue disorder that makes measurement of standing height and armspan measurement inaccurate.

c. Armspan

Armspan is defined as the maximum distance from the tip of the middle finger of one hand to the tip of the same finger of the other hand with outstretched arms and the subject standing erect. It is measured when patients stand erect, with their back against the wall (URL 6). All readings were taken to the nearest 0.5 cm using a measuring tape.

d. Weight

Body weight was measured with a calibrated precision scale (SECA) with subjects wearing indoor clothes but without coat and shoes. The calibration was carried out by the company engineers on yearly basis.

e. Body Mass Index (BMI)

BMI values were derived by dividing weight in kilograms (kg) by square of height (metres).

f. Smoking History

Information on smoking status was obtained from each patient by asking about his/her current smoking status i.e. were they a current smoker, ex –smoker or non-smoker. If the patient was a smoker or ex-smoker, additional information was asked including when he/she had started smoking, how many cigarettes they had smoked/day and when he/she stopped smoking.

Pack Year History

Pack years = Number of cigarettes smoked / 20 x no of years smoking.

In other words, one pack year is equivalent to 7300 cigarettes smoked (i.e. 20 cigarettes smoked per day for 1 year divided by 20).

Passive Smoking History

This was obtained by asking the patient about smoking exposure he/she has/had over their whole life. Therefore, questions were used to obtain this information. These were as follows.

1. Did either of your parents smoke?
2. Where did they smoke (inside home/living room, smoking area in home, outside home, garden)?
3. How many years had he/she lived with them?
4. When married, whether spouse or partner was a smoker, where they smoked (inside home/living room, smoking area in home, outside home, garden)?
5. How many years had he/she lived with his/her partner?
6. Information about any work-related smoking exposure and duration were also obtained.
7. Finally, all the years he/she had been exposed to smoke were added to derive a total number of passive smoking years.

g. Historic occupation details

This information was obtained by asking the patient about his/her work history and any related exposure at his/her work place including asbestos, chemicals and welding to determine industrial pollution exposures.

h. Current Medication

The information about medication history was obtained from patients' prescription slips and inhalers that they were instructed to bring along to the recruitment session at the hospital.

i. Lung Function Measurement

Spirometry

Spirometry was performed using a Vitalograph (Model No: 2120). Before the actual test was carried out the name, age, gender, date of birth, height, weight, BMI and ethnic group were entered in the computer. These details were used to calculate predicted values as per the ATS guidelines.

The calibration of the spirometer was carried out by the researcher on a daily basis. Calibration was performed with a 3L syringe following a standard procedure for calibration (Clausen et al., 1982).

Patients were requested not to take any long acting bronchodilators for up to 24 hours and no short acting bronchodilators for at least 8 hours prior to the day of visit. After confirmation, the pre-bronchodilator readings were obtained, then an inhaled dose of salbutamol (400µg) *via* a spacer was administered and the spirometry repeated, after 30 minutes, to record post bronchodilator response of the airflow. The bronchodilator was not given to patients with normal spirometry (FEV_1 % predicted $\geq 80\%$) and FEV_1/FVC ratio $>70\%$.

Predicted values were obtained with the help of the regression equation proposed by the European Respiratory Society (ERS) guidelines (ERS, 1993).

For Males: PREDICTED FEV₁ = (4.30 x height) – (0.029 x age - 2.49)

For Females: PREDICTED FEV₁ = (3.95 x height) – (0.025 x age - 2.60)

During the test patients were asked to:

1. Sit up comfortably and straight.
2. Take a deep breath in to fill their lungs completely.
3. Place the mouthpiece of the spirometer tightly between the lips.
4. Blow the air into mouthpiece out fast, hard and as long as possible (forced expiration).
5. The test was performed three times and the highest value of FEV₁ and FVC recorded.

j. Fat Free Mass

The fat free mass (lean body mass) was calculated with the help of a device called Bioelectrical Impedance (BIA). The detailed of how it works is discussed in section below:-

Bioelectrical impedance Analysis (BIA)

BIA is a simple procedure that can be performed at home or in the clinic in a matter of minutes. The analyser calculates tissue and fluid compartments using an imperceptible electrical current passed through pads placed on one hand and one foot as the subject lies comfortably.

The body composition was measured using the latest technology of Bioelectrical Impedance Analysis (BIA) using Bodystat 1500 MDD (Figure 3.1). This model was recommended as appropriate for the study (Wouters, personal communication, March 2007).

Features

- Dual frequency
- Self-calibrating



Figure 3.1. Bodystat 1500 MDD

Lean tissues (muscles and bones) are better conductors of electricity than adipose tissues. So, when a very low electrical current passes through the body (about one tenth on an AA battery) the percentages of fat and muscle tissues can be calculated from the recorded impedance, body weight and height.

The data required to measure composition were keyed into the Bodystat unit. The disposable electrodes were then attached to the patients' ankles and wrists and the crocodile/alligator clips were connected to the exposed tabs on the Bodystat electrodes (Figure 3.2). Lastly, the Enter key on the instrument was pressed. The test takes no more than 20 second to complete and a list of values related to body composition are displayed on the LCD screen within seconds.

Display Information

- Fat Mass
- Fat %
- Lean body mass / Fat Free Mass
- Dry Lean Weight

- Total Weight (kg, lb., st/lb.)
- Total Body Water
- Basal Metabolic Rate (BMR)
- BMI
- Waist/Hip Ratio

All the information was then transferred to the patient's report form in the specified section of the questionnaire

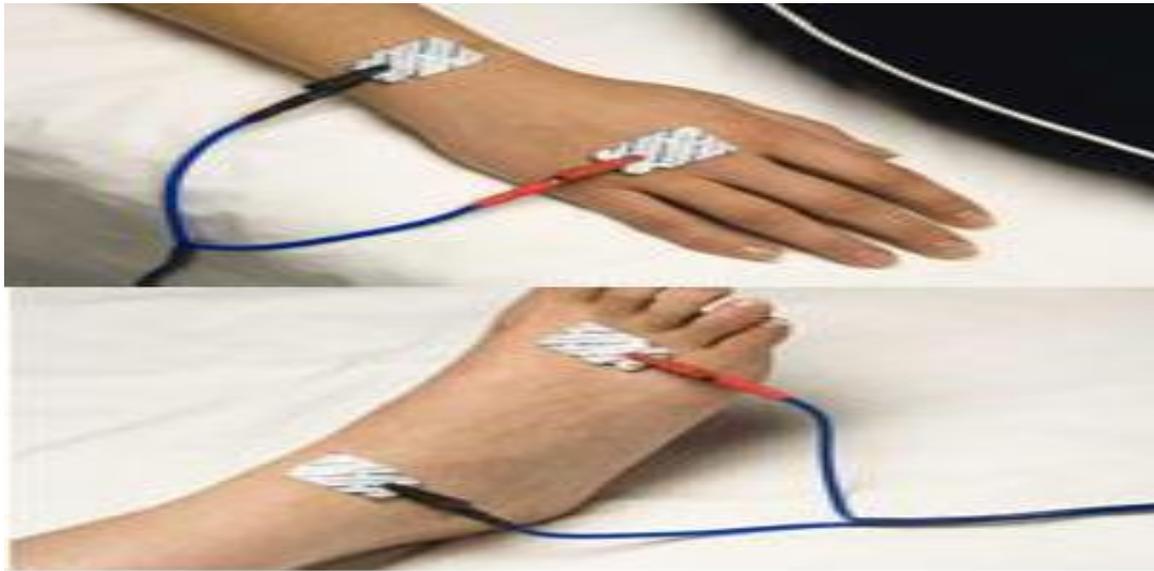


Figure 3.2. The sites of electrodes and crocodile/alligator clips on ankles and wrists.

The unit has built in calibration procedures. The system measures bio-impedance on a whole body basis.

k. Six Minute Walk Test (SMWT)

The SMWT involves measuring how far the patient can walk in 6 minutes, whilst walking at their own pace, resting if, when and for as long as necessary. It is used to determine exercise tolerance.

It is usual for a subject to undertake a practice walk followed by the actual test. After the practice six-minute walk test, the patient was allowed time to recover (for 30 minutes) before doing the second test (Celli, et al., 2004).

The walk test took place in a corridor with a measured ten metre distance marked on the floor. Subjects walked up and down the course and the total distance and the number of times they stopped together with oxygen saturation and pulse rate were recorded. While resting between the walk tests, subjects were asked to complete the Respiratory Questionnaire, historic residency questionnaire, and a work history was also obtained by means of a brief questionnaire composed by the researcher.

1. Hand-grip strength

Hand grip was measured using a Jamar Hydraulic Hand Dynamometer - 12-0600 (Figure 3.3). The Jamar hand-grip dynamometer allows measurement of the muscle strength of both hands (Fess, 1987). After explaining the importance of measuring grip strength and the proper method of holding the hand dynamometer, the values of grip strengths (left hand, right hand and/or dominant hand) of each patient were measured on three occasions and the highest value was recorded. A standard position (sitting in a straight-backed chair) and procedure recommended by the American Society of Hand Therapists (Richards et al. 1996) was used to measure hand grip strength in our study subjects. Medical reports were checked to find any history of joint disease, trauma or any other medical condition that could alter the values of hand grip measurements. The percent predicted values were calculated for dominant hand grip strength, using reference values for the dominant hand according to respective age and gender (Sunnerhagen et al., 2000).



Figure 3.3. Jamar Hydraulic Hand Dynamometer - 12-0600

m. Physical examination

A full physical cardiovascular and respiratory assessment of the patient was carried out to exclude any un-diagnosed or newly developed signs of any comorbidity, signs of oedema (pitting or non-pitting), atrial fibrillation, heart sounds, breath sounds, wheezing, crackles, clubbing, and anaemia).

n. Blood Samples for High Sensitivity C Reactive Protein (High Sensitivity CRP)

After explaining to participants the reason and method used to take blood samples, a consent form was given to the patient to sign and after obtaining the signed consent form for the blood test, 3 cms³ of blood was drawn from the most prominent vein in the arm or hand by inserting a needle.

Blood Collection Procedure

All recommended precautionary measures were taken before, during and after the blood sampling. The patient's vein was punctured with a sterile needle attached to an aspirating

device. This allows the drawing of venous blood with the least amount of patient discomfort and trauma.

o. SGRQ (St. George's Respiratory Questionnaire)

Disease-specific instruments relate more closely to clinical symptoms and, as a consequence, may be more acceptable for clinicians (Marcia, 1996). In recent years, several studies have reported results of HRQL instruments such as Chronic Respiratory Questionnaire (Guyatt et al.; 1987) or Seattle Obstructive Lung Disease Questionnaire (SOLDQ) (Tu, 1997) specific for respiratory patients. These instruments have been developed in English-speaking countries and include several health status measures for asthma patients (Cook et al., 1993; Hyland et al., 1991; Marks et al., 1993), one for COPD patients (Guyatt et al., 1987; 1989), and one designed for use in patients with COPD and/or asthma (Jones, 1991&1992). Most of these measures have been shown to be reproducible, valid and responsive, although they differ from each other in several respects. The SGRQ is a validated questionnaire to measure HRQL in patients with COPD (Ferrer et al., 1996; Jones, 1992).

The questionnaire used in this research was arrived at after the following screening protocol:

1. Is it valid? Can its validity, reliability and authenticity be demonstrated on the basis of a literature review?
2. Is it globally accepted? As this research mostly involved elderly people, the questionnaire should be easily completed and short.
3. Is the questionnaire disease specific? The present research only involved COPD patients and generic questionnaires often fail to detect small differences among COPD patients.
4. Is an English version of the questionnaire available?
5. Is it likely that patients will be able to complete the questionnaire in the available time?

The SGRQ appeared to be the most appropriate questionnaire according to the study protocol. Permission to use SGRQ has been obtained *via* email from its author, Professor P.W. Jones in St. George's Hospital, London, UK.

The SGRQ is widely used for the assessment of health status in patients suffering from chronic airflow limitation.

SGRQ is a pre-validated questionnaire developed by Jones (1992), which is a disease specific questionnaire particularly for COPD sufferers (Jones, 1992). It is used extensively to measure different domains: disease symptomatology, the impact of the disease on life style and activity levels of the patients.

The SGRQ scoring system ranges from 0 (no disability / no health impairment) to 100 (severe disability or worst health status).

Topics covered by the SGRQ

The SGRQ contains 50 items (covering 76 levels) divided into three components or domains: The first component is "Symptoms" which consists of 8 items, including questions about respiratory symptoms, their frequency and severity; the second is "Activity". This contains 16 items, and the questions are related to activities impaired due to chest symptoms such as breathlessness; finally the third component is "Impacts" composed of 26 questions, which covers a range of aspects concerned with social functioning, activities of daily living such as going out for shopping, gardening and psychological disturbances resulting from airways disease.

Each item in the questionnaire has a weight attached, which provides an estimate of the distress associated with the symptom or state described. These weights were collected in 140 asthma patients and they were shown to be applicable to a wide range of patients with asthma or COPD because demographic and disease-related factors had minimal influence on them (Jones et al., 1991). A score was calculated for each subscale of the SGRQ and also an overall score was calculated following procedures and handling of missing data recommended by the developer (Jones, personal communication, September 2007).

The questionnaire has been shown to be reproducible and valid (Jones et al., 1992). Furthermore, in a head-to-head comparison, it was shown to be more responsive to differences in disease severity than the Sickness Impact Profile (SIP) which is a generic questionnaire

(Okubadejo et al., 1997) to measure COPD severity. In patients with COPD, who had a mean FEV₁ of 50% predicted, SGRQ scores are normally distributed around a mean of 50, which is indicative of good scaling properties (Burge et al., 2000).

Scores for SGRQ domains are on a 100 - point scale. Higher scores correspond to a worse quality of life (Table 2).

SGRQ Components	POSSIBLE SCORES
SYMPTOMS	0-100
ACTIVITY	0-100
IMPACT	0-100
TOTAL SGRQ	Symptoms Score + Activity Score + Impact Score

Table 3.1. SGRQ domains and their score range.

The SGRQ score ranges from 0-100 where

HIGH SCORE suggests low Quality of life

LOW SCORE suggests high Quality of Life

In almost all previous studies, in which the SGRQ questionnaire has been used (Ferrer et al., 2002; Miravittles et al., 2004; Torres et al., 2006) scores were expressed in percentages for all domains.

p. Medical Research Council Dyspnoea Scale

The members of the cohort were given the scores and their definition and asked to classify themselves. The score they assigned to their illness was recorded.

The MRC is a validated tool to measure functional status of patients due to dyspnoea according to the activities impaired. The MRC scores are classified into five grades on the basis of limited activities due to shortness of breath as shown in table 3.2.

MRC Score	ACTIVITY LIMITED DUE TO DYSPNOEA
1	Shortness of breath with strenuous exercise
2	Shortness of breath when hurrying on the level or walking up a slight hill
3	Walking slower than people of the same age on the level because of breathlessness or having to stop for breath when walking at own pace
4	Needing to stop after walking 100 yards on the level.
5	Too breathless to leave the house or breathless when dressing or undressing.

Table 3.2. MRC Scores and activities impaired associated with each score.

Bestall and colleagues (1999) investigated the usefulness of this scale in COPD patients and concluded that the MRC Dyspnoea Scale showed a significant relationship to exercise performance, health status, mortality and other outcomes being independent of lung function data. The score ranges from 1 to 5. Patients with MRC grade 5 represents maximum disability due to shortness of breath (Fletcher, 1960).

The MRC dyspnoea score is now widely used in Britain and it is accepted internationally (Celli, 2004).

q. Charlson Index

The index consists of a list of 19 chronic, life threatening clinical conditions as shown in table 3.3. Each condition has an associated score (1 or 2), taken from the original Charlson paper (Charlson et al., 1987, Valderas et al., 2009). The scores are based on the adjusted risk of one-year mortality.

Any associated clinical condition can interfere with the prognosis of a patient with COPD and therefore play a vital role in determining progression, recovery and improvement in patients' overall health condition.

Co-morbidity	Present	Points
Myocardial Infarct		1
Congestive heart failure		1
Peripheral vascular disease		1
Dementia		1
Chronic pulmonary disease		1
Connective tissue disease		1
Ulcer disease		1
Mild liver disease		1
Diabetes		1
Diabetes with end organ damage		2
Hemiplegia		2
Moderate or severe renal disease		2
2 nd solid tumour (non metastatic)		2
Leukaemia		2
Lymphoma, multiple myeloma		2
Moderate or severe liver disease		3
2 nd metastatic solid tumour		6
AIDS		6

Comments

Total points _____

Optional Extension

Age	Present	Score
50-59		1
60-69		2
70-79		3
80-89		4
90-99		5

Total combined score _____

Table 3.3. Charlson Co-morbidity Index

The researcher took the detailed history and performed a physical examination of the study subject in order to find out any co-existing condition subjects may have and if the researcher found that the subject had any obvious pathology listed on a comorbidity index chart (Table 3.3) that column was marked and then the total score was recorded. For example if patient has signs of congestive heart failure (pedal oedema, crackles) he/she possess a Charlson index score of 1 or comorbidity score of 1.

3.6 Data Analysis

All statistical analysis was carried out using Statistical software package (SPSS version 16.0 prior to July, 2011 and version 17.0 after that). A p-value of <0.05 was considered significant. The data used in this study have a wide range of varieties include continuous, categorical, nominal, ordinal and discrete and therefore various tests have been involved in data analysis.

a. Basic Statistical Tests

b. Advance Statistical Test

a. Basic Tests

The list of tests is presented in table 3.4.

Tests	Parametric	Non Parametric
Difference between two groups	Independent t test	Mann Whitney U test
Difference between more than two groups	ANOVA	Kruksal Wallis Test
Difference between individuals (measured twice)	Paired T test	Two Related sample
Difference between individuals (measured more than two times)		K Related sample
Relationships	Pearson	Spearman Rank

Table 3.4. Basic statistical tests used in data analysis

b. Advanced Statistical Testing.

b.1. Chi Square Test

The Chi-Square test can be used as a test of association between the categorisation which allows the comparison of two attributes in a sample of data, to determine if there is any relationship between them. In this research, this test was used determine the proportion of males and females in categories of smokers, exsmokers and non-smokers.

b.2. Kaplan-Meier Survival Analysis (KMSA)

The Kaplan-Meier Survival Analysis (KMSA) procedure is a method of estimating time-to-event models in the presence of censored cases (Kaplan and Meier, 1958). Censored cases are those cases for which the second event is not recorded (for example, study subjects still survived at the end of the research study). The Kaplan-Meier model is based on estimating

conditional probabilities at each time point when an event occurs and taking the product limit of those probabilities to estimate the survival rate at each point in time.

In this study, the KMSA was employed to further assess the ability of different severity indices to predict outcomes. KMSA curves are generally used to represent outcomes that are times to an event (Kaplan, 1984, Hersh et al., 2004); in this study the event is death. In the present study they have been utilized to examine the probability of study subjects surviving over ten years and to represent the proportion of the study population continues to survive. As the number of subjects in the deceased group decreases over time, the curves are more precise in the earlier periods (left hand side of the survival curves) than later periods (right hand side of the survival curves) (URL 7).

Another important advantage of the KMSA curves is that the method can take into account some types of censored cases/data (when the value of a measurement or observation is only partially known), particularly right-censoring, which occurs if a patient withdraws from a study, i.e. is lost from the sample before the final outcome is observed. In other words, incomplete data also contribute to the model. On the graphs representing KM curves, small vertical lines along the distributing curves represent losses, where a study subject's survival time has been right-censored.

b3. Cox Regression

This method was used to examine how multiple potential prognostic factors (such as age and pack years) may predict the probability of outcome-free “survival” over time and therefore influence the main predictor of interest.

This helps to develop predictive scores for time-to-event data. The model produces a survival function that predicts the probability that the event of interest has occurred at a given time for given values of the predictor variables (for example BOD and GOLD scores in present study). The shape of the survival function and the regression coefficients for the predictors are estimated from observed subjects; the model can then be applied to new cases that have measurements for the predictor variables. It is also noticeable that information from censored subjects, that is those that do not experience the event of interest during the time of

observation, contributes usefully to the estimation of the index in presence of other potential indicators of the outcome of interest.

Cox regression analysis was therefore employed as it is a useful test for modelling the time to a specified event, based upon the values of difference covariates. A covariate is defined as a variable or a group of variables that is possibly predictive of the study outcome (Last, 2001). A covariate may be of direct interest or it may acts as a confounder. The analysis of the data shows that inclusion and/or exclusion of the covariate or group of covariates allowed improved estimates of the trend against time to be obtained compared to analyses which omitted the covariate (Fox, 2002; Cox, 1972). The potential covariates in the present study mainly include age, gender, smoking history and comorbidities for the different assessment models.

b4. ROC Curves

This procedure is a useful way to evaluate the performance of classification schemes in which there is one variable with two categories by which subjects are classified. It is assumed that increasing numbers on the assessed index represent the increasing belief that the subject belongs to one category, while decreasing numbers on the index of interest represent the increasing belief that the subject belongs to the other category.

In the present study, the Receiver Operating Characteristic (ROC) curves were utilized to determine the appropriate cut-off values of the different COPD clinical indicators of mortality. The sensitivity and specificity were also determined for each variable. To discriminate subjects who are at higher risk from those who are at lower risk, this was commonly quantified by measuring concordance, the “c statistic”. “c” statistic is similar to the area under the ROC curve (Hanley and McNeil, 1982). C varies between 0.5 and 1.0 and for sensible models; the higher the value the greater the sensitivity of the model.

B. Qualitative Analysis

3.7 Introduction

The wellness study was an extension of a study examining the natural history of a cohort of COPD patients identified in 1999-2002. In order to control the progression of chronic diseases like COPD it is believed that physical and physiological assessment are not enough to monitor disease progression (Han et al., 2010). It is therefore may be necessary to assess the attitude and/or psychological status (wellness status) of the sufferers to control COPD progression and to improve outcomes.

An initial objective in an exploration and assessment was to design a wellness questionnaire; the second objective was the identification of those members of the cohort who were still alive in December 2010, so that the questionnaire could be sent to survivors.

Steps of the Wellness Part of the Study

This part of the study involves 4 major steps aimed at designing a validated questionnaire and using it in a cohort of COPD patients to assess their wellness status (figure 3.4). These steps are described below in detail.

Step 1. Pool of questions

The first step of the study was to develop a pool of questions that would be used to assess wellness status. These were mainly based on a literature search as well as review meetings with project supervisors.

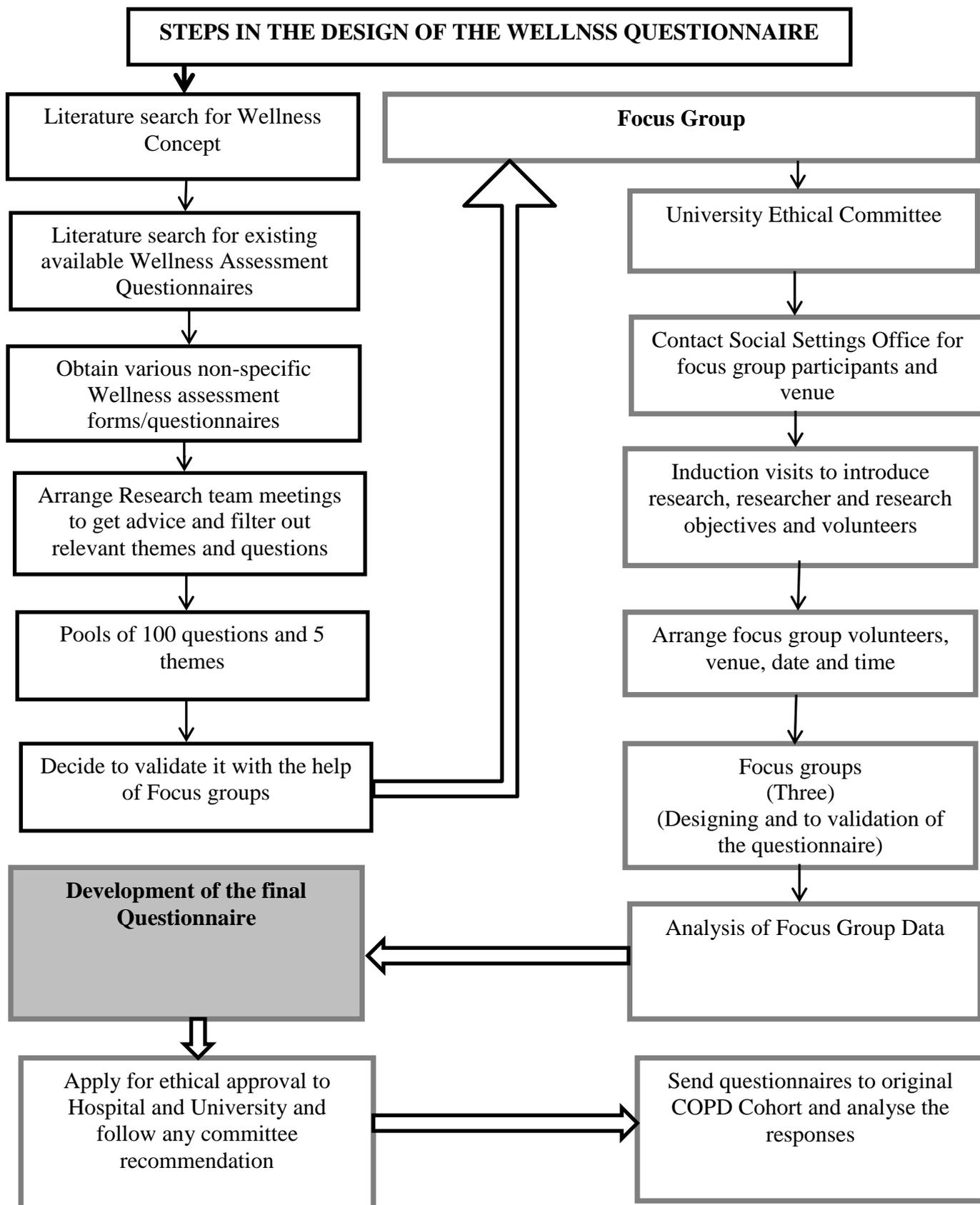


Figure 3.4. Schematic Representation of the Steps taken to Design a Wellness Questionnaire

Step 2. Designing and Validation of the questionnaire

The design opted to carry out a focus-group to examine the quality, character, reliability and validity of the data obtained. In the present study the researcher took account of various important aspects to conduct a result oriented focus group, as indicated in previous studies (Morgan, 1988). The most vital is the size of the groups. It is recommended that 4-10 participants are the most appropriate numbers (Morgan, 1988; Kruger and Casey, 2009) although in developing countries focus groups tend to be larger in size (8-15 people) (Kumar, 1987).

The need, assessment, design, validation, and application of a wellness questionnaire for use in the study were completed in following stages:

Focus Group Sessions

A. Focus Group I (Age Concern, Sunderland)

In the present research, before carrying out wellness study in patients, it was opted to carry out focus groups (Seymour, 2004). The focus group were scheduled in neutral venues external to the hospitals to encourage receptivity during the sessions (Mordan & Scannel, 1998). The focus group adds authenticity to the newly developed Wellness questionnaire.

For this purpose, the Sunderland Age Concern office was contacted and all the details about the research were explained. Initially, Age Concern Sunderland branches were attended and an address made lasting 15 minutes in which the research and the purpose of the research were explained by the author. Then a request was made for people to volunteer for the focus group. The focus group was finally arranged with those who agreed to participate and a later date and venue was finalized after mutual agreement between author, participants and administration of the Age concern Office, Sunderland.

During the focus group, the purpose and rules of the focus group were explained to the participants, namely the need for a wellness assessment in COPD and the design of the questionnaire to evaluate this issue.

The opportunity was then given to each participant to introduce himself/herself to the other participants and moderator and also to ask about any concerns/questions regarding the discussion topic or any other relevant query about the conduct of the focus group. The participants were also informed about the audio-recording of the session and its purpose. After their agreement, the formal focus group discussion commenced.

The discussion was started with an initial question to seek the participants' views on how they feel and think about assessing wellness status as opposed to health status.

The second question asked about their thoughts on what they believe is necessary for being mentally and physically healthy. They were asked if they were aware of the reasons, solutions and the ways of identifying and improving their current state of health and wellbeing.

They were asked if they considered a lifestyle was healthy because of lack of disease or if it is possible to have a disease and still feel well because of taking regular medication and attending regular follow-up medical visits. Thus they were asked if they truly understood the concept of wellness.

The information gathered concluded that the term 'wellness' encompasses a wide range of parameters.

The focus group aimed to discuss and gather general public comments from the same age range as the original study cohort and examined:

- 1. Question Purpose/Themes**
- 2. Question Content and Wording**
- 3. Response Format**
- 4. Question Sequence**
- 5. Questionnaire Lay out**

Hard copies of the questionnaires (developed from step 1) were distributed to the participants with a request that they read the questionnaire (for 30 minutes) and the formal discussion was started once they had finished reading. A pen or a pencil was provided to each participant. Tea, coffee and biscuits were also provided to the participants. As recommended,

the whole focus group discussion was recorded after taking consent from each participant at the venue.

In addition to audio-recording, comprehensive notes were also made during the discussion session.

B. Focus Group II (Breathe Easy Group, Primary Care Trust, Sunderland)

After successful completion of Focus Group I at Age Concern, modifications were made to the wellness questionnaire based on the feedback, advice and comments of the participants; a reformed version of the wellness questionnaire was then developed and a second focus group was scheduled to discuss this modified version of the questionnaire. This group of people had breathing problems such as COPD, asthma, pneumoconiosis, and mesothelioma. This was a “Breathe Easy” group.

The Breathe Easy group runs under the management of the British Lung Foundation (BLF). It is a charity set up to raise funds and awareness for people with respiratory disease. The group consists mainly of people who suffer from lung disease, such as COPD, bronchiectasis and pneumoconiosis. In the second phase, the modified questionnaire was presented to the “Sunderland Breathe Easy Group”, in order to gain feedback from a cohort with similar respiratory conditions to the study population. The session was held at the Primary Care Trust, Sunderland.

The purpose was to conduct a focus group in a Breathe Easy setting to gather further views on the designed Respiratory Wellness Questionnaire. This focus group added their views and general comments; this helped to validate the design, composition and contents of the questionnaire.

The focus group aimed to discuss and gather the opinion of “expert patients” on different dimensions of the questionnaire including themes and purpose of the questions included in the questionnaire..

Hard copies of the questionnaires (modified after the first focus group) were distributed to the participants with a request that they read the questionnaire (for 20 minutes) and the formal discussion was started once they had finished reading. A pen or a pencil was provided to each participant. Tea, coffee and biscuits were also provided to the participants. The whole focus group discussion was also recorded after taking consent from each participant at the venue.

In addition to audio-recording, comprehensive notes were also made during the discussion session.

The questionnaire was then amended based on the discussion and feedback from this group.

C. Focus group III (Breathe Easy Group-South Tyneside)

After carrying out Focus Group I and II , the recommended modifications were made in the wellness questionnaire based on feedback, advice and comments of the participants; the reformed version of the wellness questionnaire was then developed and a third focus group session was scheduled to discuss the modified/final version of the questionnaire. The main aim of this session was to get comprehensive and specific comments of the public with breathing problems on the designed questionnaire.

For this purpose, Breath Easy group South Tyneside was contacted and an initial visit was made by the author of this study to introduce himself, the study and to recruit the volunteers for the third focus group. The date for the focus group session was then agreed and two days prior to the session, the author contacted the agreed participants again just to remind the members of the date, time and venue of the focus group session. The session was held at Physiotherapy Section, South Tyneside Hospital, South Tyneside.

All the steps of conducting the focus was followed as indicated in focus group I and II discussion above. The whole session was recorded.

This focus group helped to further validate the contents of the questionnaire.

Step 3: Modifications and Amendments in the Questionnaire

All three focus group discussions were very open, composed, result oriented and helpful and all the recommendations based on focus group member views were again discussed with the project supervisors and changes were made accordingly.

Step 4: Use of the questionnaire in the Surviving members of the cohort

Ethical approval was then obtained from all of the relevant ethical approval bodies at the hospital as well as the University of Sunderland.

The changes were again made as per the recommendations of the Ethical approval committees and a final version was developed. The final version of the wellness questionnaire was sent to the survivors of the cohort to examine wellness along with an invitation to participate, consent form, information sheet, and instructions on how to fill in the questionnaire, together with an enclosed pre-paid and addressed envelope. The questionnaires were collected back from participants *via* post.

The members of the group who did not respond were again contacted by the author in case they had not received the questionnaire or in case if they needed help. The questionnaires were again sent to those who had not received it or lost it after receiving it but, were willing to participate.

3.8 STUDY INSTRUMENT

3.8.1 Wellness Assessment Questionnaire

To determine wellness perception, a questionnaire was required. However, there is no validated tool for use in COPD patients. There are many wellness forms available from different bodies and on different websites that are nonspecific or related to health insurance or lifestyle advice.

They all contain the following domains: diet habits, weight control, exercise, mental health and overall fitness level. None of the questionnaires addresses specific issues related to COPD.

It was therefore essential that novel questions be constructed for use in COPD patients in order to explore the relationship between COPD and wellness that would be reliable and could be used in different clinical settings.

The Wellness Questionnaire title “Sunderland Respiratory Wellness Questionnaire” (SRWQ) (see appendix 2) has been used. This questionnaire consists of 5 thematic sections given below:

1. Personal/Physical Wellness
2. Emotional Wellness
3. Self-Responsibility Related Wellness
4. Mental Wellness
5. Spiritual Wellness

Each section contained 10 statements related to the patient’s wellbeing and 4 options were given of which patients had to tick one option that they think reflected their wellness most appropriately and scores range from 1 to 4 were given against each response. Therefore a person could score a minimum of 10 and a maximum of 40 in each domain. A low score indicates a low wellness and high score reflects better wellness status on that particular section.

As there are 5 sections in the questionnaire, the minimum score in total would be 50 and maximum would be 200. The score towards a higher side of the scale represents better overall wellness status in study subjects.

In addition to quantitative assessment of wellness with the help of scores, the SWRQ also contains empty spaces/box at the end of each section where the study subjects could write additional comments where necessary. Instructions to write additional comment was given on the title page of the questionnaire (see SRWQ in appendix 2).

3.8.2 Reliability and validity

The data of the focus-group can be tested for reliability very effectively by comparing the responses of first focus groups with the second (Bender & Ewbank, 1994). In the present study this was carried out by conducting the third focus group, which was similar to the second focus group as well as the original study cohort in terms of their age ranges, gender mix, health problems and interaction among the respondents. Therefore the responses of the third focus group to the designed questionnaire was helpful in validating the contents, composition and other important factors that are related to a newly-developed questionnaire (Bender & Ewbank, 1994).

3.8.3 Statistical Analysis for Qualitative Data

To analyse focus group data, “content analysis” is employed. In order to carry out content analysis on text (transcribed from audio files/hand written notes) that is generated as a result of the focus group, the text is either coded or broken down into meaningful categories on the basis of a word, sentence or a phrase used that makes sense and later themes can be generated on this basis. The final stage is to examine the text using one of content analysis' basic methods: conceptual analysis or relational analysis (Bender & Ewbank, 1994). In the present study conceptual analysis (which is also known as thematic analysis) was used to analyse focus group data.

The steps followed to analyse focus group data are summarized in figure 3.5.

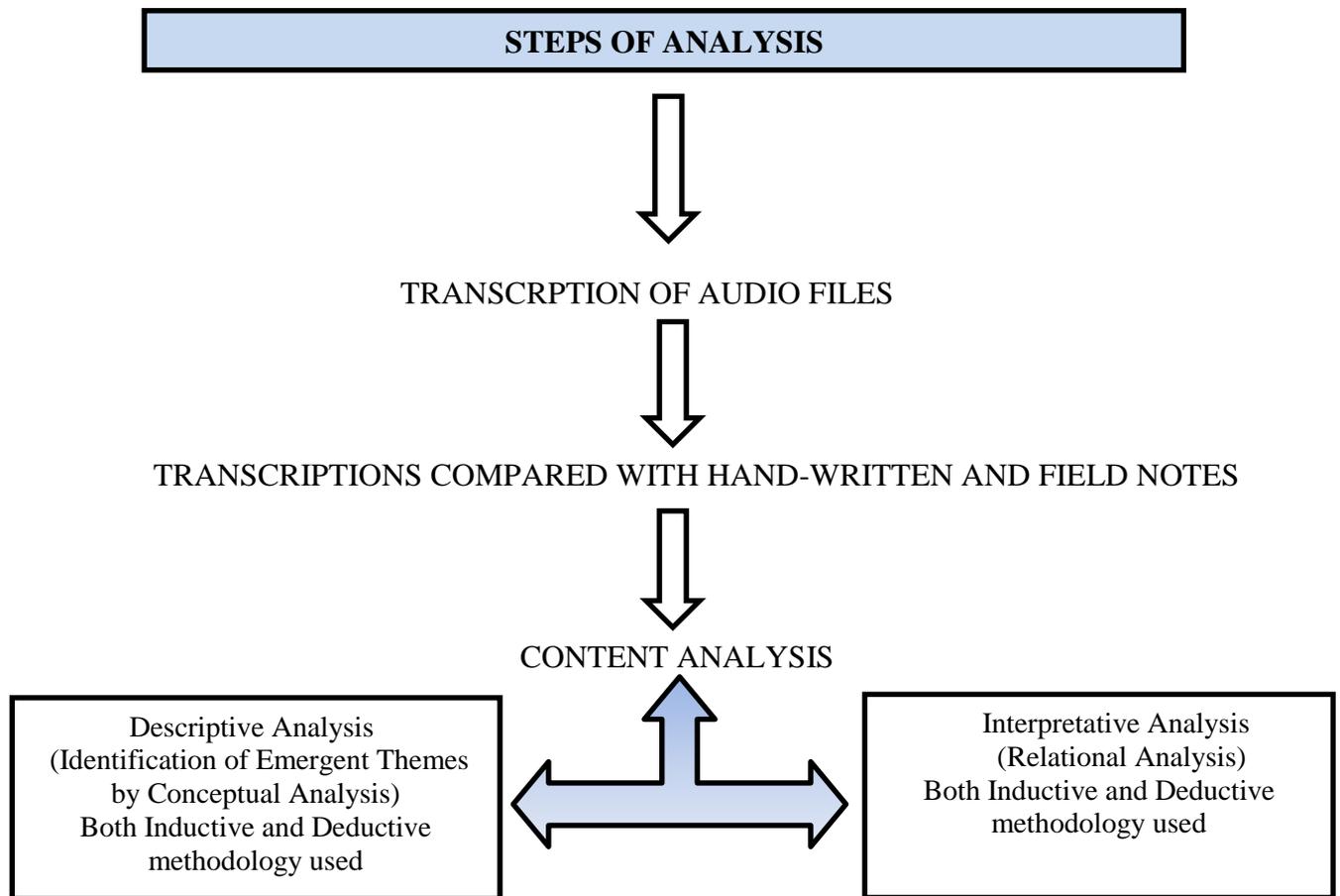


Figure 3.5. Stages of Focus group analysis

3.8.4 Content Analysis

Content analysis helps to identify the frequency of certain phrases within transcribed or hand-written notes produced from focus groups. The identified phrases or concepts help to draw sensible, reasonable and meaningful conclusions with respect to research aims and objectives. (Weber, 1990). It is suggested that content analysis also helps in determining the emotional and psychological state of an individual or groups and allow describing any behavioural response to communication (Weber, 1990; Berelson, 1952; Krippendorff, 2004 and 2008).

Content analysis methodology can be carried out by following either of its two main categories which are closely related to each other.

A. Conceptual Analysis (Thematic Analysis)

B. Relational Analysis

A. Conceptual Analysis (Thematic Analysis)

This type of content analysis helps to identify different concepts mentioned in the text. The conceptual analysis allows the researcher to identify groups of words, sentences or statements which lead to a specific concept, meaning or conclusion (Weber 1990; Krippendorff, 2004 and 2008). It also gives the researcher the opportunity to look at the text content of the data related to a theme or area of interest, tally its frequency of occurrence in transcribed literature or hand written notes and enables the researcher to draw a meaningful conclusion.

B. Relational Analysis

The relational analysis mainly builds on the facts generated as a result of conceptual analysis examining the relationship on the basis of the concepts in the text. Thus relational analysis is an interpretation of the conceptual analysis in order to find meaningful relationships between occurrences of meaningful concepts (Weber, 1990; Krippendorff, 2004 and 2008).

3.8.5 Inductive and Deductive Approaches

In the present study both the inductive and deductive methods are used to analyse focus group data. It is recommended that the inductive content analysis is an acceptable approach in research where no previous studies are available that deal with the phenomenon (Elo and Kyngas, 2008), which is the case in the present study of wellness.

Similarly, the deductive approach was also utilized to analyse data because one study suggests that is useful if the general objective of the study was to test an existing theory in a different situation (Elo & Kyngas, 2008) and in the present study the phenomenon of wellness status has been tested in patients with COPD.

In this study, the researcher tries to explore in depth an understanding of a patient's psychological behaviour and how he/she perceives his/her health in terms of wellness which directly or indirectly influences the clinical condition and overall health in these patients. As discussed above, the wellness questionnaire was developed with the help of certain themes gathered from the feedback of focus groups carried out during the study.

Therefore, to analyse qualitative data a thematic approach was used. The thematic approach is the most basic yet commonly used analytical technique in qualitative data analysis (Krippendorff, 2004 & 2008).

Thematic analysis is a rarely acknowledged but a widely-used method in qualitative research. (Boyatzis,1998; Roulsten,2001). It is regarded as a foundational method for qualitative analysis. However, thematic analysis has not received detailed attention in terms of guidelines about how to carry out analysis properly (Attride-Stirling, 2001; Boyatzis, 1998). Furthermore, many researchers have given some really useful tips for carrying out a thematic analysis.

Thematic analysis is not as dependent on specialised theory as some other qualitative techniques such as Discourse analysis or Conversation analysis (Hammersley, 2003). As a consequence, thematic analysis is more accessible to new researchers who are unfamiliar with the relevant theory in-depth (Braun & Clarke, 2006).

In thematic analysis, it is the researcher's job to identify and develop themes on the basis of text; the researcher has received, and/or transcribed from the study subjects. It is also the researcher's responsibility to associate developed themes in order to address the research question effectively. This is not so easy to do although the identification of a few superficial themes is generally quite easy, although it does not reflect the required level of analysis adequately. The "keyness" of a theme is not necessarily dependent on quantifiable measures-

but rather on whether it captures something important in relation to the overall research question (Braun & Clarke, 2006).

As recommended in data obtained from the focus group, deviant case analysis is also important (Kitzinger, 1995). In other words it is important to distinguish between group agreed points and an opinion raised by an individual, as it may give the researcher the opportunity to formulate a further hypothesis or develop a new area of research. As an example, the section on “Spirituality” was not initially present in the questionnaire draft. However, during focus group 1 session, one member of the group has mentioned that questions about the spirituality should be added in the questionnaire as an assessment of wellness, and this was later accepted and agreed by the other participants. (See result section of chapter 6 for details).

In the present study, the wellness questionnaire was used for quantitative assessment of the wellness in patients with COPD. In addition to the scores against each response, the wellness questionnaire also contained an empty spaces/box at the end of each section where the study subjects could write additional comments where necessary and these comments from the study participants were then to be used to perform a qualitative analysis by developing themes on the basis of their comments and then correlate a patient’s wellness perception to their overall wellness as well as health status in study subjects.

Chapter 4

A CRITICAL EVALUATION OF THE MULTIDIMENSIONAL INDEX BOD

4.1. Introduction

COPD is a complex disease and patients with COPD experience multiple clinical manifestations that significantly impair their functional, physiological and psychological health. It has been suggested that low body mass index (Landbo et al., 1999), loss of lean body mass (Schols et al., 2005, Calverly et al., 2003), hypoxaemia or hypercapnia (Cote, 2006; Nizet et al., 2005), reduced capacity for exercise (O' Donnell & Katherine, 2008), and perceived breathlessness (Nishimura et al., 2002) assessed with the MRC Dyspnoea Score can all be used as measures of disease progression. Because of these complexities there is a poor correlation between impairment (measured as FEV₁%) (Pauwels et al., 2001) and disability as evidenced by health status, exercise capacity and dyspnoea (Figure 4.1) (Curtis et al., 1994). Therefore assessment of COPD progression needs to adopt a multidimensional approach.

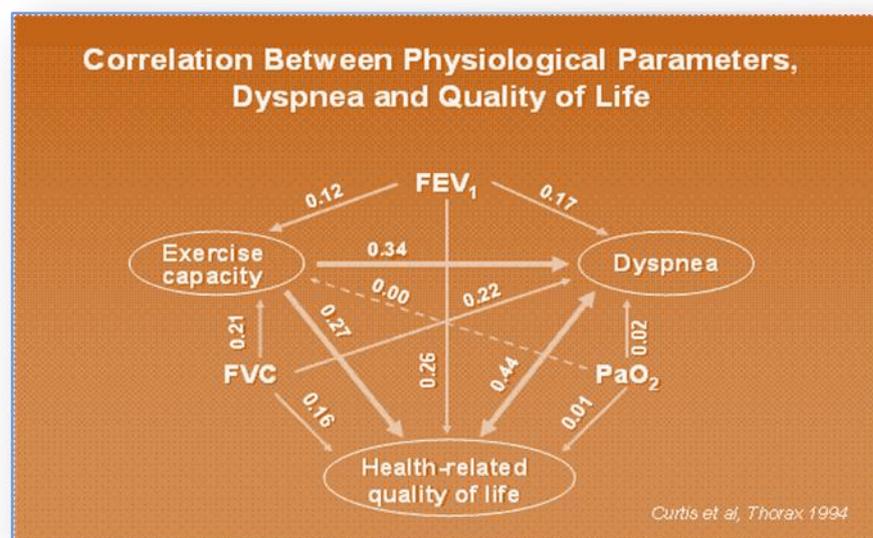


Figure 4.1. Correlations between COPD Related Measurements (Curtis et al., 1994)

Primarily based on the Fletcher-Peto model (Fletcher & Peto 1977, Figure 2.6) forced expiratory volume in one second (FEV_1) cut-off points have routinely been used to establish the severity of COPD and various guidelines have been published to classify the severity of the disease based upon this measure. These include ATS (1995), BTS (1997), GOLD (2001) and consensus guidelines from the ATS-European Respiratory Society (ATS-ERS) (2004). Esteban and colleagues (2009) compared them as prognostic indicators and although the BTS system was slightly superior, none of the guidelines was closely related to 5 year mortality.

Recently, the National Institute for Clinical Excellence (NICE) updated its guidelines to improve COPD care; it recommends using a definition of COPD based on the GOLD classification of severity of airflow obstruction (NICE, 2010). Therefore, in the present research the GOLD severity model was used to compare COPD progression and severity with the multidimensional index developed in this study BOD, to demonstrate its effectiveness in the assessment of COPD progression and mortality.

Celli and colleagues (2004) have shown that a multidimensional index, of the severity of COPD, proved to be a better predictor of mortality than FEV_1 alone. They measured Body mass index, airflow Obstruction, Dyspnoea and Exercise test and named the index “BODE”. The scoring of the BODE index is not complex; however, the exercise test (six minute walk distance) requires time and space for its measurement. Subsequently, Puhan and colleagues (2009) developed and validated another index named “ADO” (age, dyspnoea and airflow obstruction (FEV_1)). In their cohort, ADO and a rescaled BODE had a similar accuracy for risk prediction. Their study emphasised the need for careful validation of prognostic indices but it should be born in mind that age is a confounder in a prognostic tool (Celli, 2009).

The present study investigates the application of a new multidimensional index BOD (BODE without an exercise test) and has explored the efficacy of the BOD multidimensional index in the characterisation of the natural history of COPD. The results of this evaluation are presented in this chapter.

4.2. Methodology

The proposed multidimensional index BOD comprises body mass index, airflow obstruction and dyspnoea score.

-  Body mass index was calculated from body weight and height.
-  Obstruction of the airway was calculated from FEV₁ predicted values
-  Subjective severity of dyspnoea was measured by MRC dyspnoea score.

4.2.1 Calculation of Assessment Models of COPD

Table 4.1 summarizes the factors measured by the different models under investigation in this study. All the indices presented in Table 4.1 including GOLD, BOD and BODE have been examined and analysed in this chapter using the members of the cohort described in Chapter 3.

Assessment Models	Measurements Used			
	FEV ₁ % Predicted (%)	BMI (kg/m ²)	MRC Score (1-5)	Exercise Test (meters)
GOLD Stages				
I	>80	-	-	-
II	<50 to 80	-	-	-
III	30 to 49	-	-	-
IV	≤29	-	-	-
BOD Scores				
0	≥65	>21	1-2	-
1	50-64	≤21	3	-
2	36-49	-	4	-
3	≤35	-	5	-
BODE Scores				
0	≥65	>21	1-2	≥350
1	50-64	≤21	3	250-349
2	36-49	-	4	150-249
3	≤35	-	5	≤149

Table 4.1. Calculation of the Assessment Models

For example, if a patient has FEV₁ of 60% predicted (O=1), MRC score of 4 (D=2), BMI of 19 (B=1), and six minute walk test of 265 meters (E=1) his/her total scores calculated from these models would be 2, 4 and 5 according to GOLD, BOD and BODE respectively.

In the BOD model, the same scoring system (Table 4.1) is utilised as is used in BODE (Table 3.4; chapter 3) but without the exercise component. The range of possible scores is 0-7. For further analyses these scores were grouped into categories (Table 4.2) as there were insufficient deaths to use individual scores to validate the index as a prognostic indicator.

BOD Scores	Categories
0-1	1
2-3	2
4-5	3
6-7	4

Table 4.2. BOD Scores and their respective Categories

Please refer to Chapter 3 section 3.1 for details of the methodology for each measurement.

4.2.2. COPD and Cause-Specific Mortality

In this study the effectiveness of the BOD Index has been assessed using the mortality of the members of the cohort. However there are a number of limitations to this approach.

COPD is a clinical condition associated with high morbidity (Yeo et al., 2006; Lang et al., 2010) and mortality (Gudmundsson et al., 2006). It is predicted that death due to COPD will rise from the sixth leading cause of death to the third leading cause by 2020 (Murray et al., 1997). A 22-yr follow-up of 5,542 adults in the first National Health and Nutrition Examination Survey (NHANES I) found that 47.7% of patients with severe COPD at baseline had COPD listed on the death certificate and 23.1% had COPD as the underlying cause of death (Mannino et al., 2003).

However, the determination of the actual cause of death in patients with COPD is controversial. Hansell and colleagues (2003) carried out a study based in England and Wales of COPD patients and suggest that the use of underlying cause of death underestimates the contribution of chronic lung disease to mortality in these patients when compared with deaths that had resulted from myocardial infarction.

In a more recent study (McGarvey et al., 2007; Ekstrom et al., 2011) explored this issue in 911 patients with COPD and suggest that COPD and pneumonia are the most common causes of death in these patients (35%). Other common causes were cardiovascular (26%) followed by

lung cancer (14%). Furthermore, no consensus has been developed in relation to deaths caused by or related to COPD. This contrasts to other diseases such as coronary artery disease. Therefore studies show a range of causes that contribute to death in these patients (Zielinski et al., 1997; Lange et al., 1990, Nussbaumer-Ochsner et al., 2011). These causes mainly include cardiovascular disease, pneumonia and lung cancer due to the higher prevalence of smoking in COPD patients that in turn leads to other life threatening comorbidities such as coronary artery disease that lead to fatal outcomes (Zielinski et al., 1997).

For this reason, death from all causes was recorded in the study participants with COPD in this study.

4.2.3 Data Analysis

There were a number of limitations to the data analysis carried out in this section of the study. One limitation was that data for the BODE index were not available for all three timeframes (1999-2002; 2007-2008; *and* 2008-2009). The reason was that the initial database was established in 1999-2002, at a time when the BODE index had not yet been published. Whilst the measurements were recorded on three occasions over a period of 10 years i.e. time 1 (1999-2002), time 2 (2007-2008) and time 3 (2008-2009), on occasions there were some missing data. Also, since data collection was undertaken over a period of 10 years, a diminishing sample size due to drop-outs occurring can be anticipated during the study. The sample size was reduced further when data were sub-divided into survivors and deceased COPD patients (Table 4.13), in order to compare the assessment models of COPD severity and progression.

The normality of the datasets was checked using the Kolmogorov-Smirnov test and histograms. Most of the tests were statistically significant (< 0.05) which suggests violations of the assumption of normality (Pallant, 2007). The histogram plots are attached in the appendices (appendix 1) of this thesis.

The paired sample t test, two related sample tests: (Wilcoxon) and K-related sample test (Friedman Test) were used to compare different monitors of progression (GOLD, BOD and

BODE) recorded on three occasions, in study subjects (including survivors with COPD and deceased COPD patients), measured at different times.

Kaplan-Meier survival curves (K-M curves) are generally used to represent outcomes that are timed to an event, in this case the event being death (Kaplan, 1983). In the present study they have been utilized to examine the probability of study subjects surviving over ten years and to represent the proportion of the study population still surviving. Because the number of subjects in the deceased group decreases over time, the curves are relatively more precise in the earlier periods (left hand side of the survival curves) than in later periods (right hand side of the survival curves) (URL 7).

Furthermore, Cox regression analysis was employed which is a useful test for modelling the time to a specified event, based upon the values of difference covariates. A covariate is defined as a variable or a group of variables that is possibly predictive of the study outcome (Last, 2001). A covariate may be of direct interest or it may act as a confounder. Analysis of the data shows that inclusion and/or exclusion of the covariate or group of covariates allows improved estimates of the trend against time to be obtained compared to analyses which omitted the covariate (Everitt, 2002). The potential covariates in the present study mainly include age, gender, smoking history and comorbidities for the different assessment models.

Additionally, in this study, the Receiver Operating Characteristic (ROC) curves were also utilized to determine the appropriate cut-off values of the different COPD clinical indicators of mortality. The sensitivity and specificity were also determined for each variable. Discrimination of subjects who are at higher risk from those who are at lower risk is commonly quantified by measuring concordance, the “c statistic”. “c” statistic is similar to the area under the ROC curve (Hanley & McNeil, 1983). C varies between 0.5 and 1.0 for sensible models; the higher the value the greater the sensitivity of the model.

All the data were analyzed using SPSS Version 16.0.

4.3. Results

A. DATA ANALYSIS OF THE COHORT STAGE 1 (1999-2002)

4.3.1. Data Collection

A cohort of patients (n=634) with suspected COPD was established. They were identified from asthma clinics in primary care during 1999-2002. The initial search process for establishing a database for COPD patients was carried out by the respiratory research team based at the Chest Clinic of Sunderland Royal Hospital. The inclusion and exclusion criterion for the established database is given in the methodology section. The patients on the database were again contacted in 2007 (which is the starting year of the present study) and recruitment visits were scheduled for those agreeing to participate in the study. Home visits were also scheduled for those who were not willing or who were unable to attend hospital.

Figure 4.2 shows a flow chart of the fate and involvement of the patients on the original database. Out of 634 persons, only 458 fulfilled the inclusion criteria for the present study. Of this 458, 118 had died in 2007 or before and therefore could not be recruited. This meant that 340 people from the original cohort were contacted. Of this number 158 subjects did not reply, were reluctant to participate or could not be contacted due to incorrect address details being held.

Similarly, during the 2008-2009 phase of this study, only 98 subjects were recruited because more drop outs occurred during the third phase of the study. However participating patients were able to complete the study protocol except for a small number who were not in a position to perform the six minute walk test either due to their illness and /or unwillingness.

Detailed demographics of the study cohort are presented in section 4.3.2. All data are presented as mean \pm SD (Standard Deviation) unless otherwise stated.

The details of the recruitment phase including the number of patients that were recruited, left the study and died, are presented in figure 4.2.

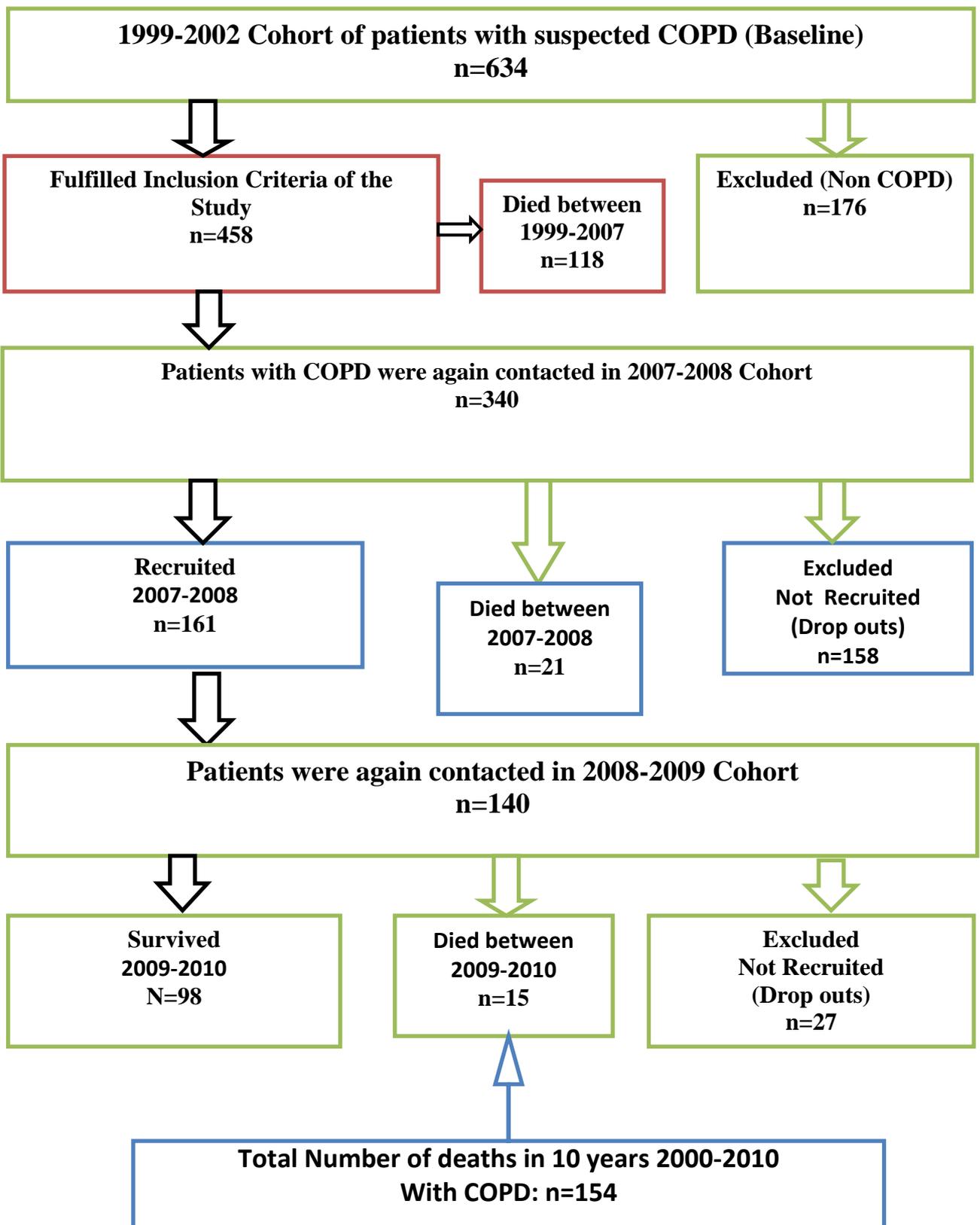


Figure 4.2. Flow chart of the recruitment phases and subjects excluded/included.

4.3.2 Subject Characteristics

The mean age of the cohort originally recruited was 64.7 ± 9.7 years, of whom 51% (n=233) were females. 87% of the cohort was either current or ex-smokers and only 13% were non-smokers. The mean pack year history was 33.0 ± 18.9 years. The BMI was 26.0 ± 5.1 kg/m². In relation to lung functions, the mean FEV₁ and % predicted were 1.53 ± 0.62 (L) and 60.9 ± 20.0 respectively indicating mild to moderate degree of severity in these patients. The subjective breathlessness as measured by MRC dyspnoea score was 2.50 ± 1.01 showing that the cohort had mild to moderate degrees of functional impairment due to shortness of breath. The detailed baseline scores of the cohort as measured by GOLD and BOD are presented in Table 4.3 and figures 4.3-4.5.

The histograms of the study variables of the present study (see appendix) indicate normally distributed data in terms of age, BMI, and pack year history (number of years smoked) in the study population in each gender.

Baseline Demographic Characteristics of the subjects (n=458)		
Age (years)		64.7 ± 9.7
Gender (m/f)	Male	225 (49.0%)
	Female	233(51.0%)
Smoking Status	Current	180 (40.6%)
	Exsmoker	206 (46.5%)
	Non smoker	57(12.9%)
Pack years (years)		33.0 ± 18.9
BMI (kg/m ²)		26.0 ± 5.1
FEV ₁ (L)		1.53 ± 0.62
FEV ₁ % predicted		60.9 ± 20.0
MRC (1-5)		2.50 ± 1.01
GOLD (1-4)		2.19 ± 0.75
Median BOD Scores (Range)		1.0 (0-6)

Table 4.3. Baseline demographics for the cohort (1999-2002). BOD scores are presented as median and range.

4.3.3 Evaluation of BOD & GOLD Models of Severity in the 1999-2002 Cohort

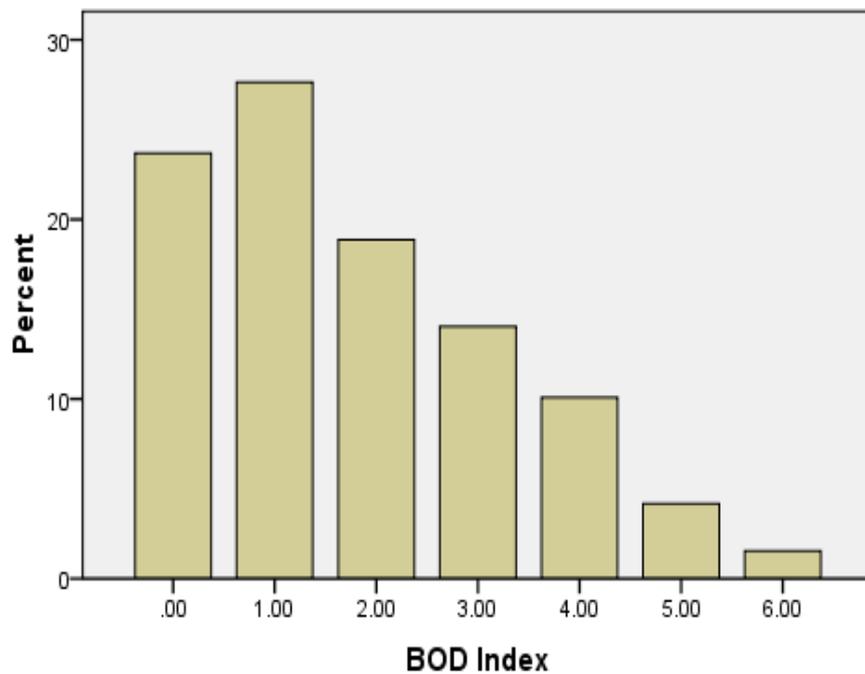


Figure 4.3. Distribution of BOD Scores in Study cohort (1999-2002)

The cohort when recruited had mild to moderate COPD as shown in figures 4.3, 4.4 and 4.5 representing the score distribution of the BOD index, BOD categories and GOLD stages respectively. More than 75% of the cohort had a BOD score of 3 or less, BOD categories of 2 or less and a GOLD score of 2 or less. It is also noticeable that the two severity indices, GOLD and BOD, indicate different degrees of severity in the same cohort. The scores observed using BOD are higher than those observed using GOLD.

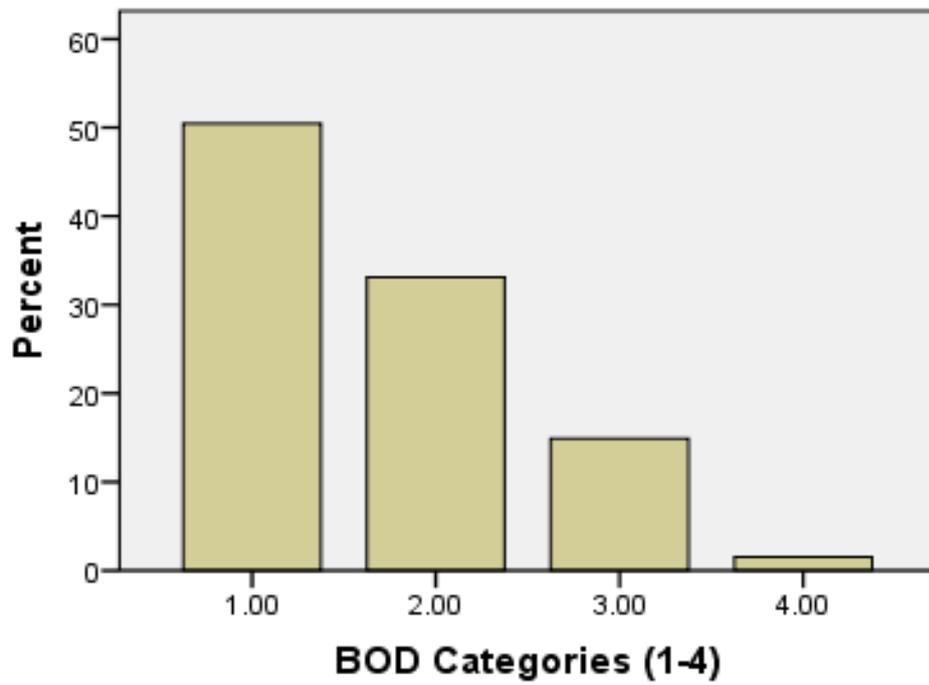


Figure 4.4. Distribution of BOD Categories in Study cohort (1999-2002)

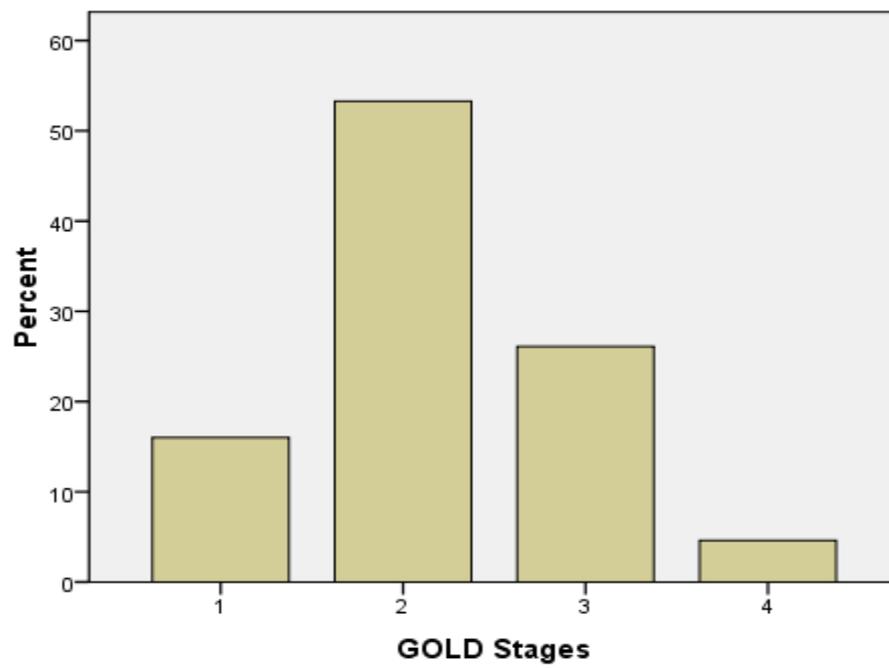


Figure 4.5. Distribution of GOLD Scores in Study cohort (1999-2002)

The measures obtained for BOD and GOLD at recruitment have been analysed further using Kaplan Meier survival curves.

In order to assess BOD as a predictor of mortality, actual BOD scores (0-7) and categories of BOD scores (1-4) (Table 4.2) were used to show the probability of survival with the help of Kaplan Meier Curves. Figure 4.6 shows that a lower BOD score represents, a higher probability of more than 10 years of survival as compared to higher BOD scores, of 5 and 6 that indicate only a 60 to 40% probability of surviving more than 10 years or more respectively. Figure 4.7, which represents the probability of survival in terms of BOD categories clearly shows that patients with BOD categories scores greater than 4 have just under a 40% chance of surviving more than 10 years. In contrast, patients with BOD categories of 0 and 1 have more than an 80 % probability of surviving more than 10 years (Figure 4.7). Figure 4.8 shows the probability of survival in terms of GOLD stages of severity (1-4), the curve shows that scores of 1-3 have 70-80% chance of surviving 10 years whereas GOLD stage 4 have a probability of 60% of surviving for 10 years.

The difference between BOD scores, BOD categories and GOLD are that the BOD scores and categories discriminate far better between individual scores and the probability of survival as compared with the GOLD scores.

As there are other factors that affect survival such as age ($p < 0.001$), pack years ($p < 0.006$), and gender ($p < 0.05$), it was decided to plot KM curves adding these factors as covariates to the BOD index.

The covariates have improved the predictive power of the index. Figure 4.10 indicates that the patients with higher BOD scores have the least chance of surviving. For example, patients with BOD category of 4 have under 30% probability to survive 10 years or more.

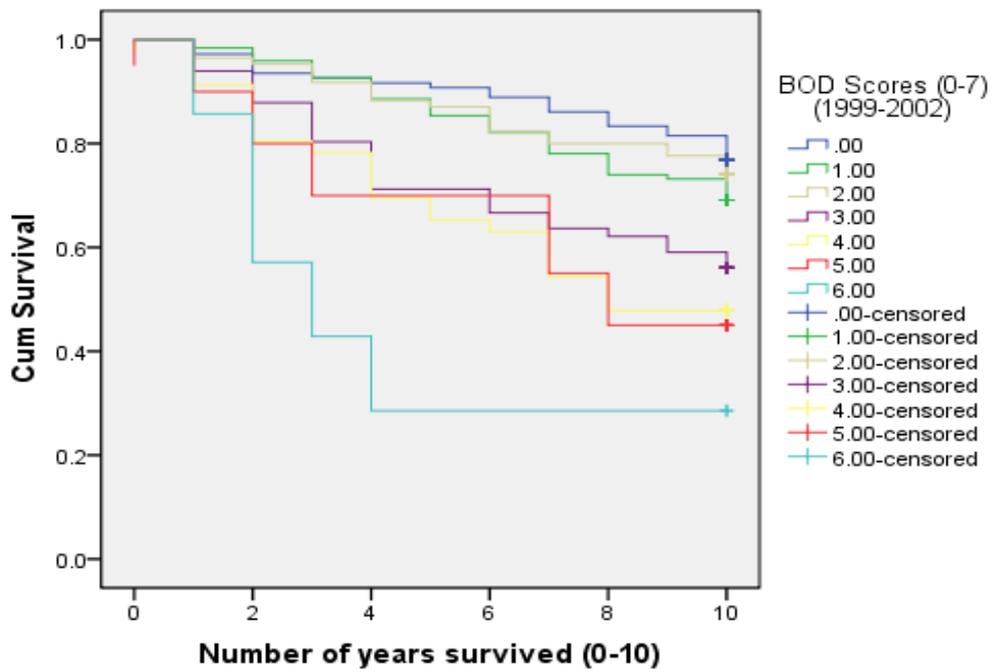


Figure 4.6. Kaplan-Meier Curve using BOD Index Scores (1999 - 2002)

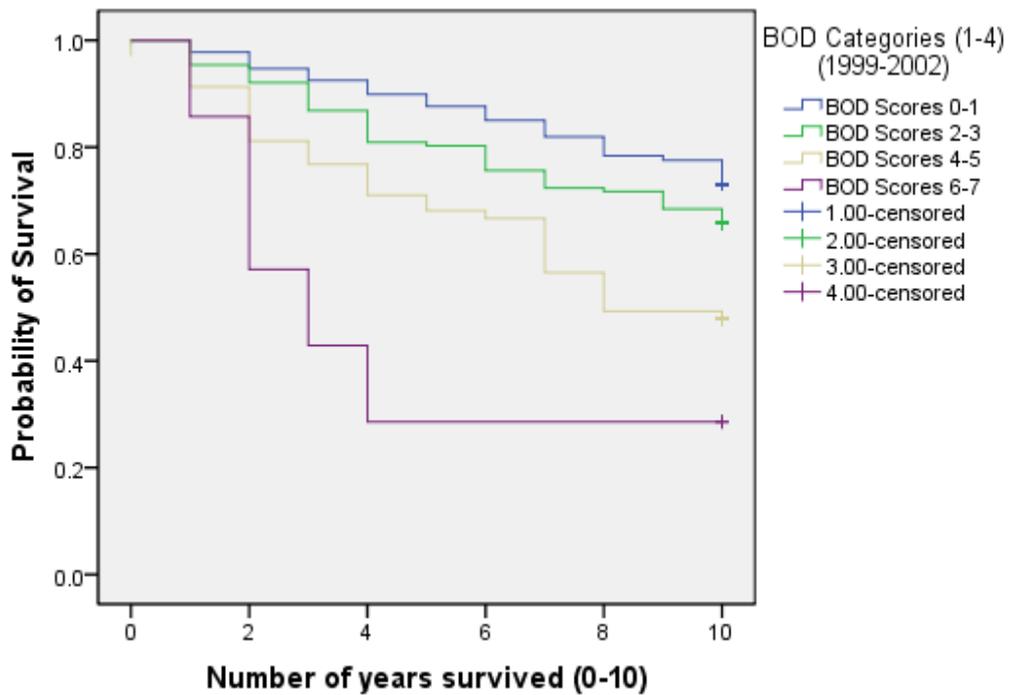


Figure 4.7. Kaplan-Meier Curve using BOD categories (1999-2002)

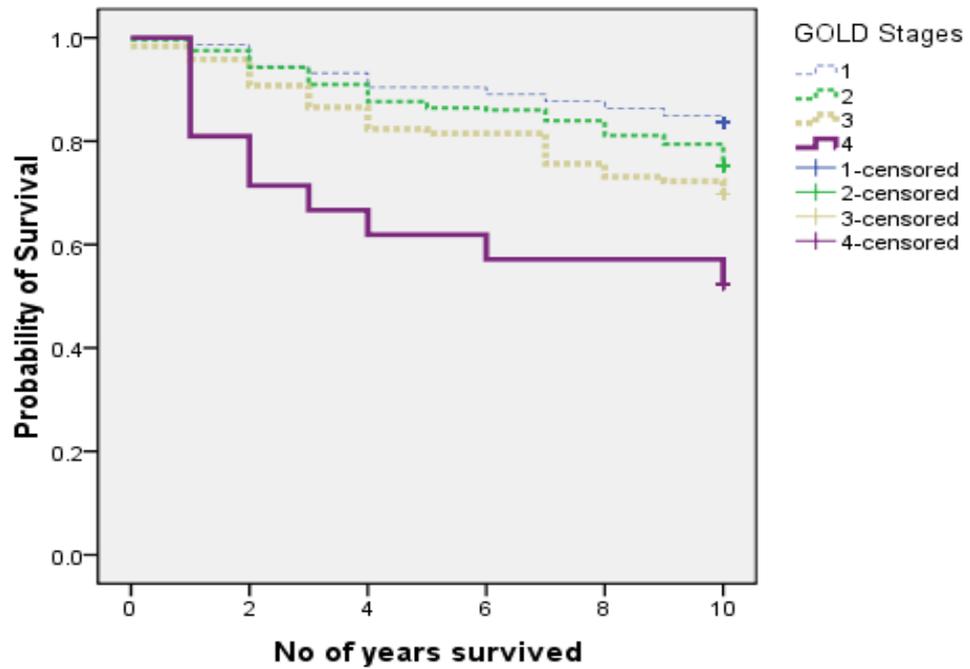


Figure 4.8. Kaplan-Meier Curve using GOLD Stages (1999-2002)

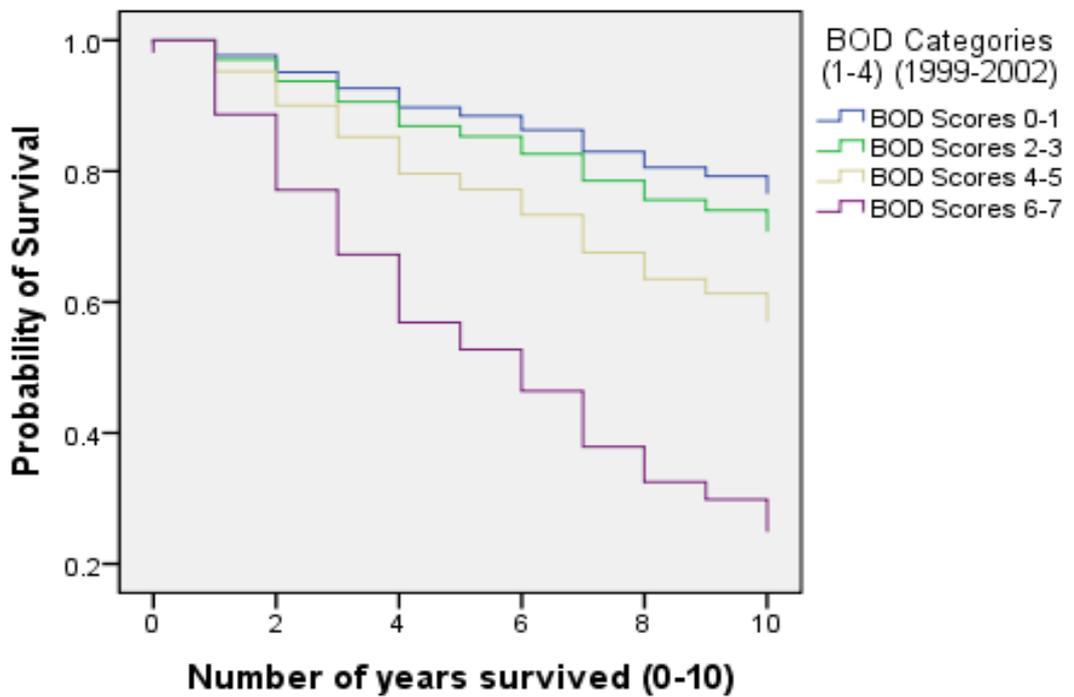


Figure 4.9. Kaplan-Meier Curve Using BOD Index with Covariates (1999-2002)

Figures 4.9 and 4.10 indicate the effectiveness of BOD categories score and GOLD severity stages in predicting 10 years survival when age, gender, and pack years were added as covariates in the model. Gender did not influence any of the indices significantly. The BOD categories 3 and 4 have lower survival curves. They are therefore more likely to have shorter times to survive. The figures also show that the sensitivity of the BOD categories in predicting survival improved (worst scores represents less probability of survival over time) by adding covariates. On the other hand GOLD stages also improved. However, figure 4.10 indicates that when covariates were added in the GOLD severity scores, they failed to differentiate survivors between stages 1, 2 and 3.

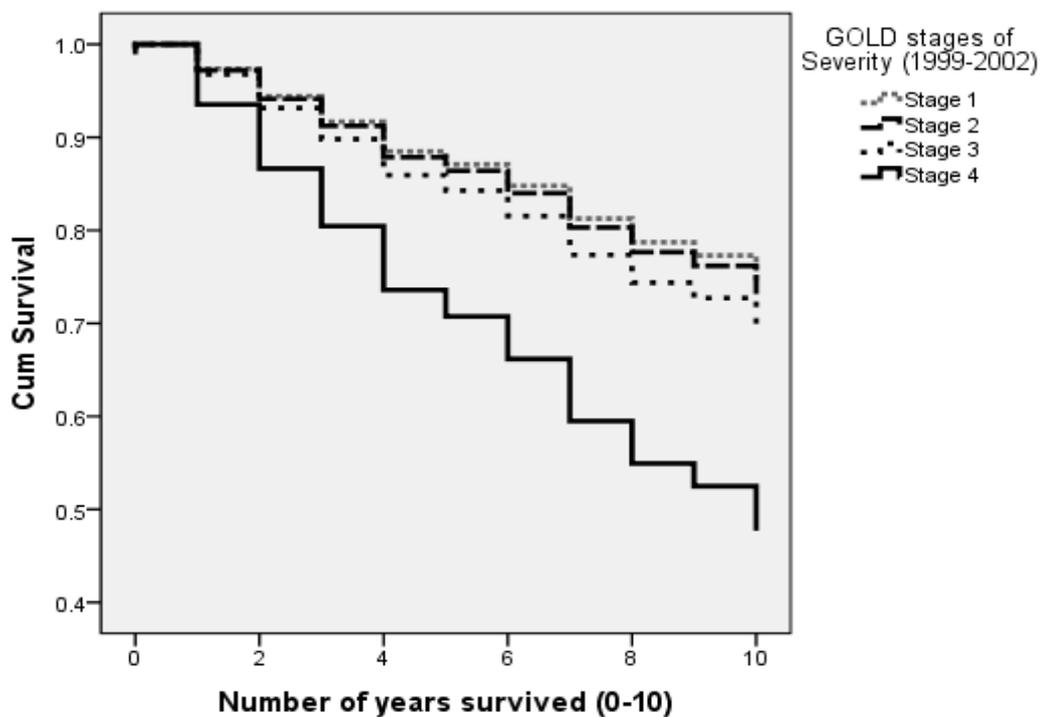


Figure 4.10. Kaplan Meier Curve of GOLD Severity Stages with Covariates (1999-2002)

In Tables 4.4 and 4.5, the Cox model (a method used to examine how multiple potential prognostic factors (such as age and pack years), that may predict the probability of outcome-free “survival” over time, was utilized to assess the ability of the BOD index and GOLD stages of severity to predict mortality. In table 4.4., the p values for age and pack years were statistically significant (<0.001 and 0.02) with positive beta values (0.76 and 0.10). The positive beta values indicate that when age (in years) increases the mortality increases and *vice*

versa. Similarly when number of years smoked increases the mortality increases and hence the B value is positive. Furthermore, BOD categories also showed a significant result ($p < 0.001$) in the presence of other prognostic variables that remained in the model, these were age and pack years. However since BOD is a categorical variable, SPSS regards the last category (category 4) as a “reference category” for the other BOD categories (1, 2 and 3). This means that as compared to category 4, patients who are in other categories (1, 2 and 3) have a lower mortality than that of those with highest BOD category (category 4) and hence these B values are negative. On the other hand, the GOLD stage ($p = 0.034$) did not have greater significance over other covariates such as age ($p < 0.001$) and pack years ($p = 0.030$) (Table 4.5).

(In order to ensure that a reliable model is build the data is split into two parts. The first part ($n = 225$) is used to build the model and the other part ($n = 233$) is passed through the model to validate it. (Appendix 1). BOD again successfully showed its superiority over GOLD in both derivation and validation cohort).

Variables in the Equation								
	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Age	.076	.010	54.227	1	.000	1.079	1.057	1.101
Pack years	.010	.004	4.876	1	.027	1.010	1.001	1.019
BOD categories			20.045	3	.000			
BOD category (1)	-1.649	.473	12.135	1	.000	.192	.076	.486
BOD category (2)	-1.392	.474	8.635	1	.003	.249	.098	.629
BOD category (3)	-.906	.482	3.528	1	.060	.404	.157	1.040

Table 4.4. The Cox regression of BOD model and covariates.

Variables in the Equation								
	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Age	.073	.010	51.987	1	.000	1.076	1.055	1.098
Pack years	.013	.004	8.862	1	.003	1.013	1.005	1.022
GOLD Stages			8.698	3	.034			
GOLD (1)	-.917	.370	6.152	1	.013	.400	.194	.825
GOLD (2)	-.862	.304	8.032	1	.005	.422	.233	.766
GOLD (3)	-.705	.322	4.796	1	.029	.494	.263	.929

Table 4.5. The Cox regression of GOLD stages and covariates.

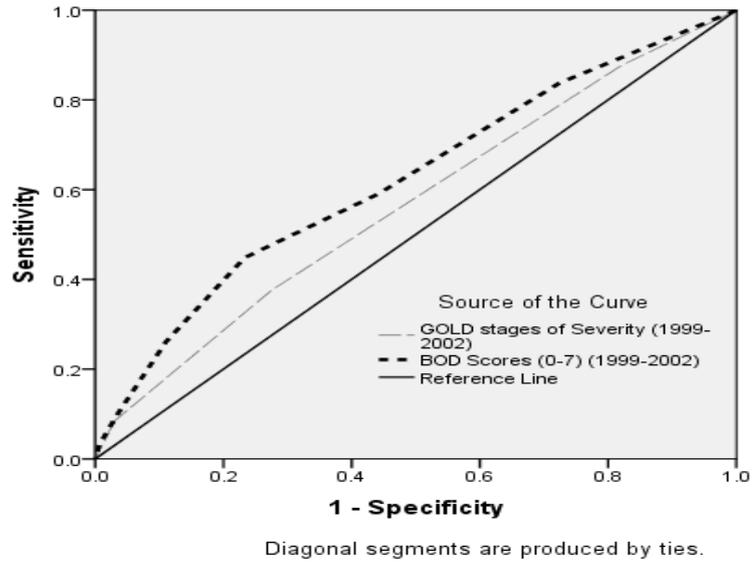


Figure 4.11. ROC Curve shows sensitivity and 1-specificity for GOLD vs BOD 1999-2002

On further analysis of the suitability of the BOD index to predict mortality in COPD, ROC curves were used to compare the capacity of these indicators in predicting health outcome using BOD (Figure 4.11 and Table 4.6). The figure and table clearly indicate that BOD works more effectively than GOLD in terms of predicting COPD mortality. The areas under the curve (AUC) for BOD and GOLD were 0.60 and 0.57 and p values were <0.001 and 0.02 respectively. In other words, neither was very good (>0.7 is optimal) as the p-value merely gives an indication of how much confidence to place in the coefficient.

Test Result Variables	Area Under the Curve	S.E	p value	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
BOD Index	0.62	.028	<0.001	.567	.678
GOLD stages of severity	0.56	.029	0.02	.512	.624

Table 4.6. ROC for different indices of COPD severity with Mortality

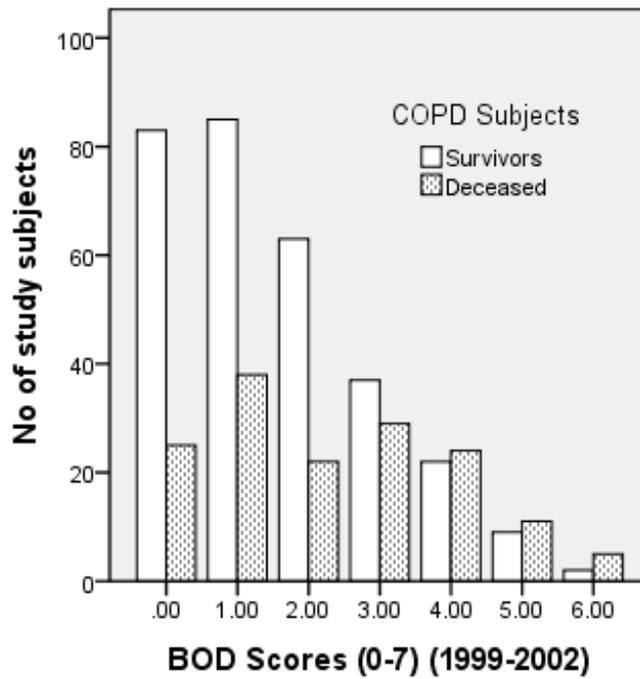


Figure 4.12. Number of survived & deceased members of the cohort in each BOD Scores

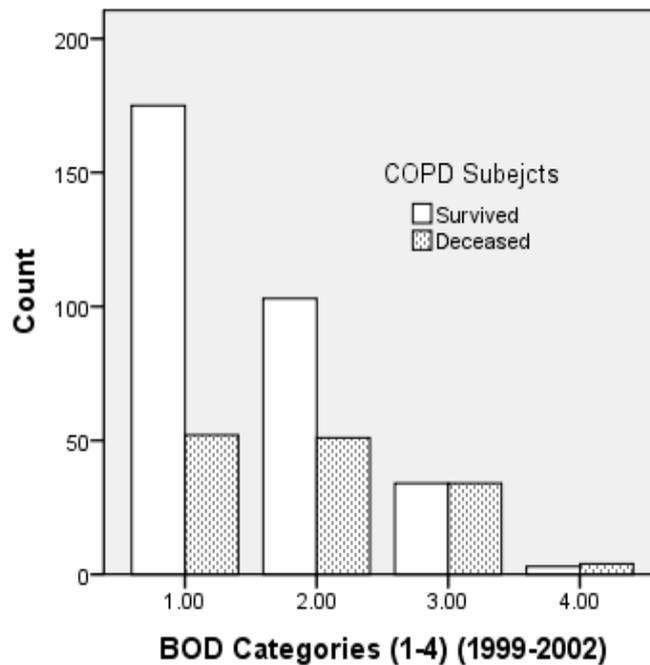


Figure 4.13. Number of survived & deceased members of the cohort in each BOD categories.

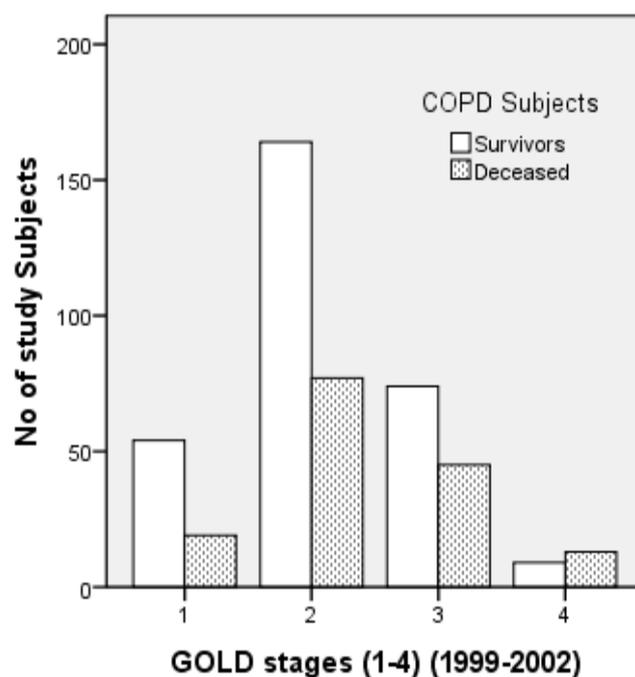


Figure 4.14. Number of survived & deceased members of the cohort in each GOLD stage

Figures 4.12, 4.13 and 4.14 above represent the percentages of patients in the study who died and survived after 10 years, in each BOD index scores (0-7), BOD Index category (1-4), and GOLD stages of severity (1-4) as assigned during the 1999-2002 phase of the study.

The figures demonstrate that the proportion of patients who survived is greater with BOD scores 0-3, BOD categories 0 and 1 than those with higher BOD scores 4-6 and categories 3 and 4. On the other hand, the proportion of subjects who died was higher with BOD scores 4-6 and categories 3 and 4 compared with patients with BOD scores 0-3, BOD categories 0 and 1. The differences are statistically significant ($p < 0.001$) for all comparisons. In contrast, GOLD stages (figure 4.14) indicates that a higher proportion of survivors are in GOLD stages 1-3 compared with GOLD stage 4 which has a higher proportion of deceased patients than survived. These figures (4.12, 4.13, 4.14) again show clear differentiations between BOD and GOLD.

B. DATA ANALYSIS OF THE COHORT AT STAGE 2 (2007-2008)

In this section of the chapter, the results for the members of cohort assessed in 2007-8 are discussed. At this time BODE has also been included in the evaluation of the cohort.

4.3.4 Subject Characteristics 2007 - 2008

Table 4.7 illustrates the demographics of the cohort at this timeframe. The cohort now comprises 51.6 % of females with a mean age of 69.3 ± 9.2 . In terms of smoking status, 38% were current smokers and 48.4 % were ex-smokers whereas only 13.5% were non-smokers. The mean pack year history was 35.6 ± 21.3 . The subjects were slightly overweight with a mean BMI of 27.1 ± 6.5 (n=21 with BMI<21) and demonstrated moderate severity in terms of spirometry with a mean FEV₁% predicted of 59.2 ± 23.1 , in terms of breathlessness with a mean MRC dyspnoea score of 3.05 ± 1.2 out of 5 and in terms of BOD and BODE index scores of 2.29 ± 0.9 and 3.22 ± 2.2 respectively.

Age (years)		69.3 ± 9.2
Gender (m/f)	Male	77 (48.0%)
	Female	84(52.0%)
Smoking Status	Current	59 (38.1%)
	Exsmoker	75 (48.4%)
	Non smoker	21(13.5%)
Pack years (years)		35.6 ± 21.3
BMI (kg/m ²)		27.1 ± 6.5
FEV ₁ (L)		1.46 ± 0.6
FEV ₁ % predicted		59.2 ± 23.1
MRC (1-5)		3.05 ± 1.2
6MWT		275.0 ± 89.4
GOLD (1-4)		2.29 ± 0.9
Median BOD Scores (Range)		2.00 (0-7)
Median BOD categories (Range)		2.00 (1-4)
BODE Scores (1-10)		3.22 ± 2.2
BODE Quartiles (1-4)		1.91 ± 1.0

Table 4.7. Demographic Characteristics of the Cohort 2007 -2008 (n=161). BOD category is presented as median and range.

The mean scores in GOLD, MRC, FEV₁% predicted, MRC, BOD and BODE indicate that the cohort had a range of disease symptoms from mild and moderate to severe.

Figures 4.15-4.19 show the score distribution of BOD, GOLD and BODE scores of severity in the study cohort. More than 75% of the cohort has a BOD score of 3 or less, BOD categories of 2 or less and GOLD score of 2 or less. It is also noticeable that the three severity indices, BOD, GOLD and BODE, indicate different degrees of severity in the same cohort. The scores observed using BOD are higher than those observed using GOLD and BODE.

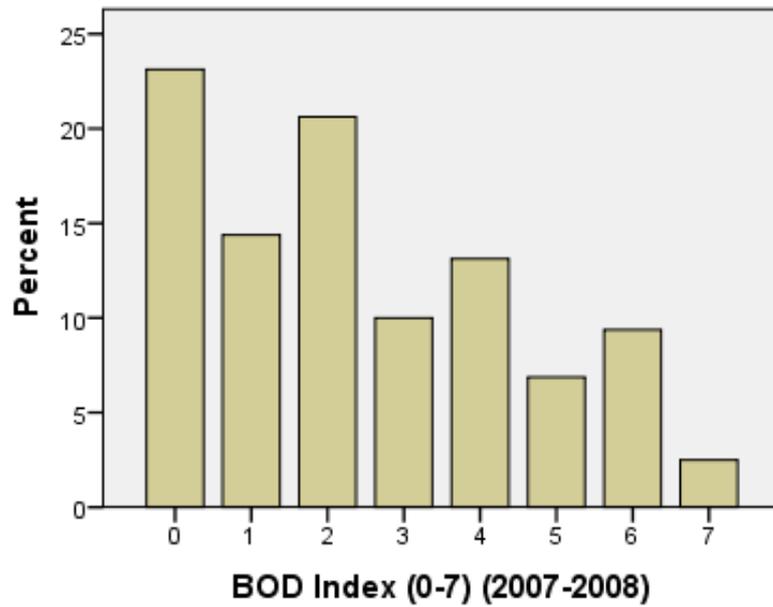


Figure 4.15. BOD score distribution (2007-2008)

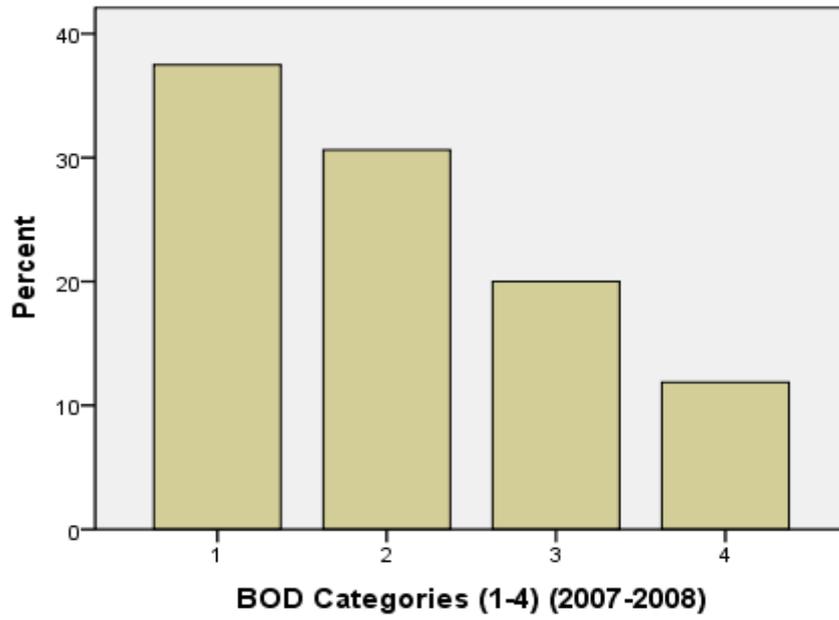


Figure 4.16. BOD categories distribution (2007-2008)

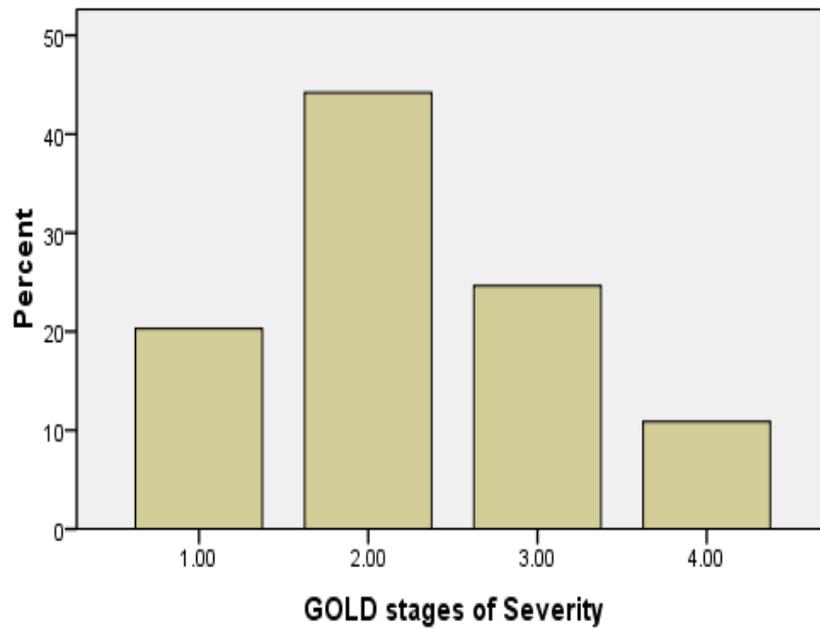


Figure 4.17. GOLD Score distribution (2007-2008)

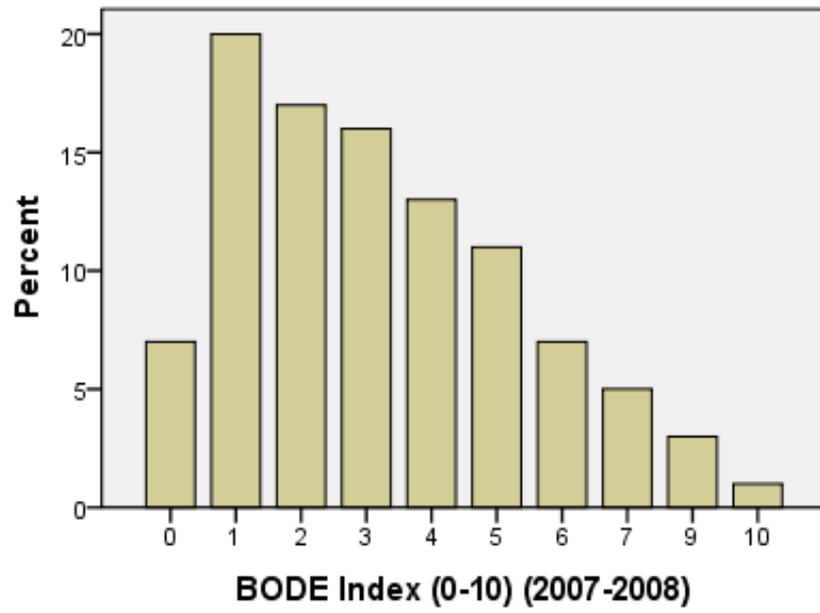


Figure 4.18. BODE Scores distribution (2007-2008)

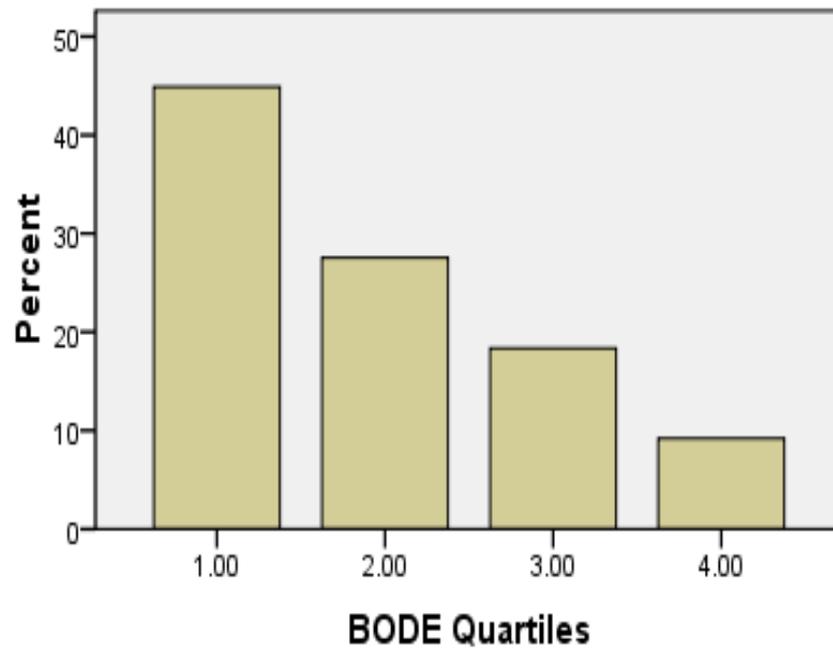


Figure 4.19. BODE quartile distribution (2007-2008)

KM curves have also been plotted in order to assess BOD, BODE and GOLD indices as a predictor of 3 year survival (2007-2010).

Figure 4.20 shows that those with the higher BOD category of 4 have only a 50 % probability of surviving more than 3 years. In contrast, patients with BOD categories of 0 and 1 have more than a 90 % probability of surviving more than 3 years (Figure 4.20).

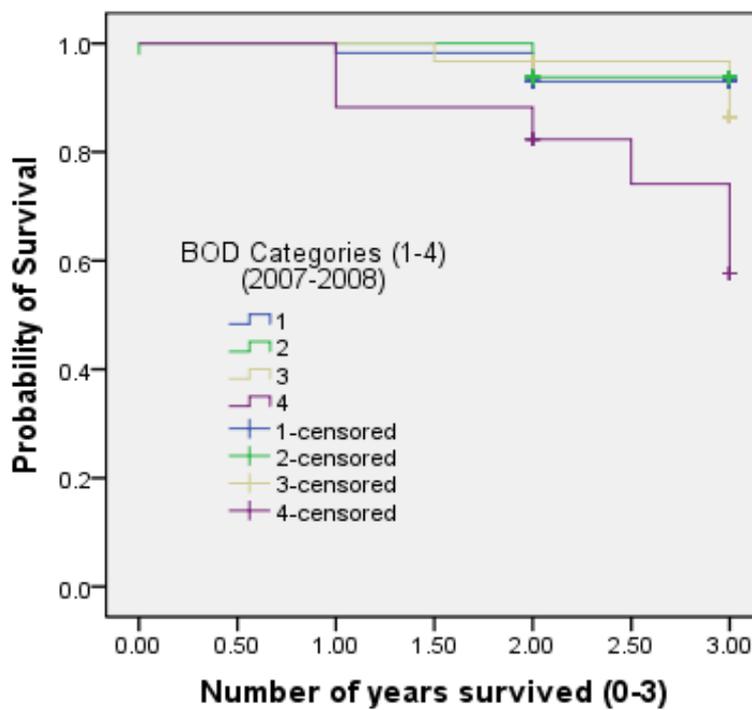


Figure 4.20. Kaplan-Meier Curve using BOD Categories (2007-2008)

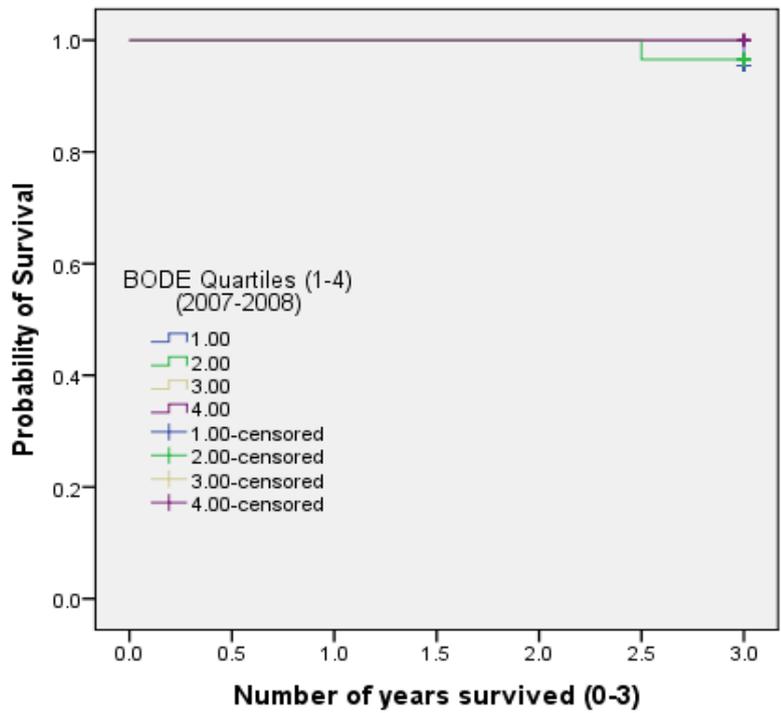


Figure 4.21. Kaplan-Meier Curve using BODE Scores (2007-2008)

Similarly, figure 4.21 represents the probability of survival in terms of BODE quartiles which did not show any significant relationship between BODE and years of survival (figure 4.21). This is may be due to the fact that only 3 deaths were observed within the group of subjects whose BODE index was recorded.

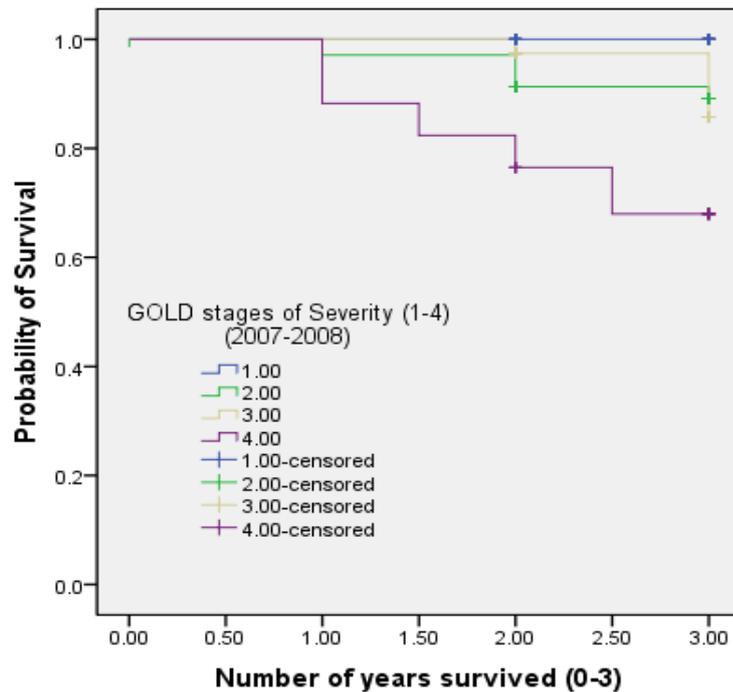


Figure 4.22. Kaplan-Meier Curve using GOLD Scores (2007-2008)

Figure 4.22 represents the probability of survival in terms of the GOLD index which indicates that higher GOLD scores may be indicative of only 66.7% of survival of 3 or more years.

Similarly figures 4.23, 4.24 and 4.25 represent the COPD severity indices when covariates were added in each index of severity i.e. BOD, BODE and GOLD. Figure 4.23 shows that the ability of the BOD index to predict mortality did not significantly alter when covariates were added.

The KM curve of BODE index with covariates did not show any particular trend (figure 4.24) because only 3 deaths were observed in patients whose BODE scores were recorded in 2007/8 cohort.

No significant effects were observed in GOLD stages 1-2 index (figure 4.25). The ability to predict mortality particularly in patients with GOLD stage 4 (very severe) diminished when covariates were added in the model.

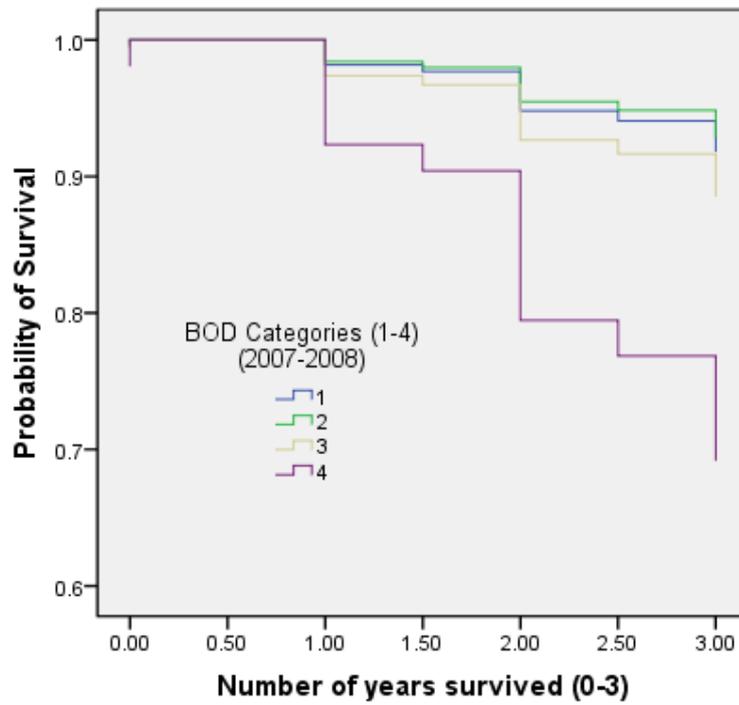


Figure 4.23. Kaplan-Meier Curve using covariates and BOD Scores (2007-2008)

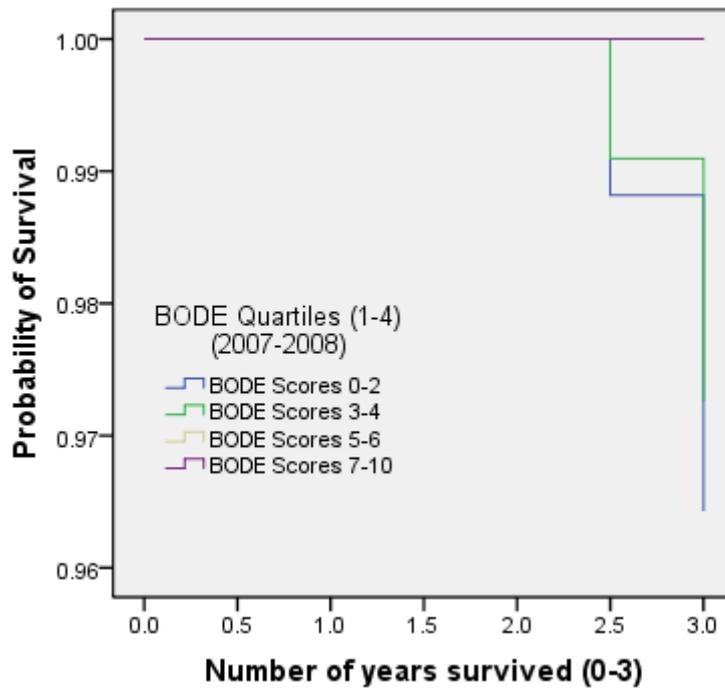


Figure 4.24. Kaplan-Meier Curve using covariates and BODE quartiles (2007-2008)

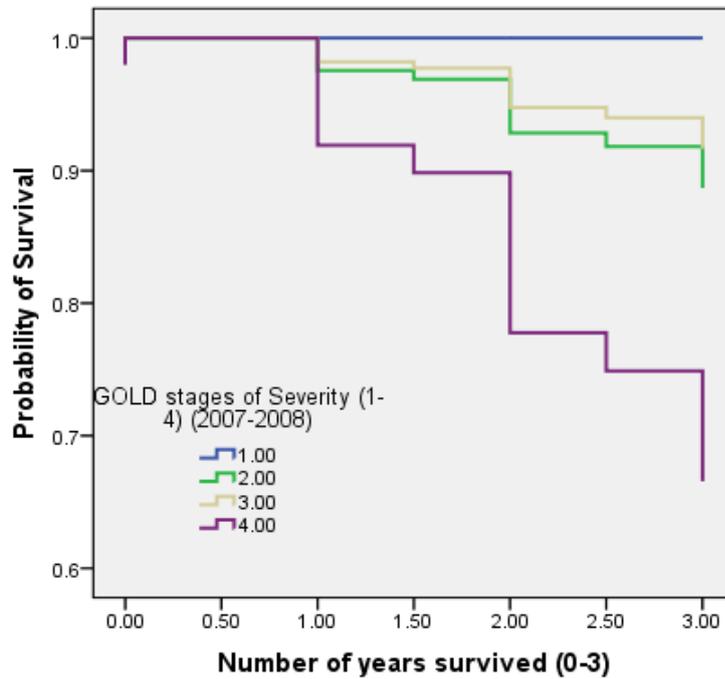


Figure 4.25. Kaplan-Meier Curve using covariates and GOLD Scores (2007-2008)

In Tables 4.8 and 4.9, the Cox model (a method used to examine how multiple potential prognostic factors such as age and pack years), was utilized to assess the ability of the BOD and BODE indices and GOLD stages of severity to predict mortality considering other factors that generally influence mortality in these patients such as gender, age and smoking history. BOD category scores 1, 2 and 3 ($p=0.04$, 0.04 and 0.05) whilst none of the other prognostic variables remained in the model. Similarly for GOLD stages 1, 2 and 3 ($p=0.03$, 0.02 , and ns respectively), none of the other covariates were significant predictor of outcome. The Cox model for BODE index was not computed due to there being fewer deaths in the cohort.

Multidimensional Index of Severity	B	SE	Wald	df	Sig.	Exp(B)
BOD categories (2007-2008)			7.185	3	.066	
BOD category 1	-1.440	.708	4.162	1	.041	.236
BOD category 2	-1.592	.765	4.334	1	.037	.203
BOD category 3	-1.621	1.119	3.831	1	.050	.112

Table 4.8. The Cox regression of BOD model and covariates (2007-2008)

GOLD Stages of Severity	B	SE	Wald	df	Sig.	Exp(B)
GOLD Stages (2007-2008)			7.563	3	.056	
GOLD Stage 1	-13.95	361.6	.001	1	.969	.000
GOLD Stage 2	-1.324	.607	4.761	1	.029	.266
GOLD Stage 3	-2.475	1.097	5.092	1	.024	.084

Table 4.9. The Cox regression of GOLD stages and covariates. (2007-2008)

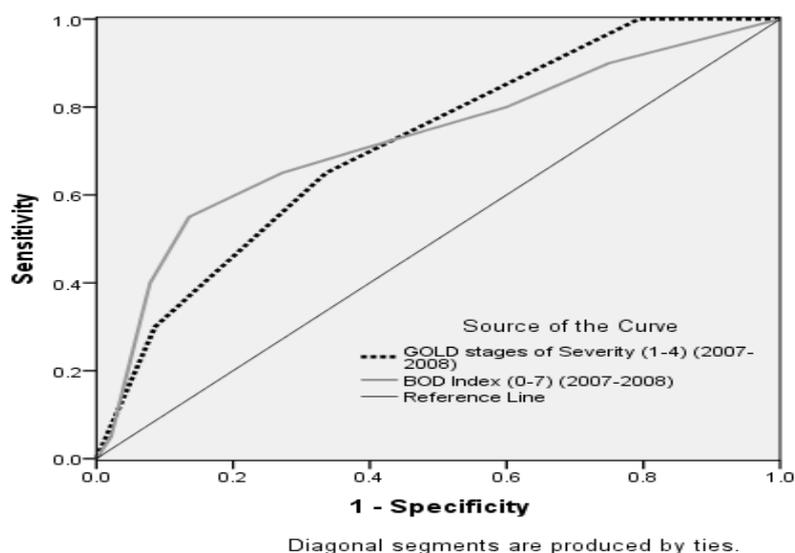


Figure 4.26. ROC Curve shows sensitivity & 1-specificity (GOLD vs BOD) 2007-2008

ROC curves were used to analyse the suitability of the BOD index and GOLD severity stages to predict mortality in COPD as shown in Figure 4.26 and Table 4.10. The figure and table clearly indicate that BOD works more effectively than GOLD. The areas under the curve (AUC) for BOD and GOLD were 0.72 and 0.71 and p values were <0.001 and 0.002 respectively. The p-value gives an indication that BOD is more accurate than GOLD.

Test Result Variable(s)	Area under curve	Std. Error	p value	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
GOLD stages (1-4) (2007-2008)	.716	.057	.002	.604	.828
BOD Index (0-7) (2007-2008)	.725	.068	.001	.593	.858

Table 4.10. Area under the curve for GOLD stages and BOD scores

C. DATA ANALYSIS OF THE COHORT AT STAGE 3 (2008-2009)

In this section of the chapter, the results for the members of cohort assessed in 2008-9 are discussed. At this time BOD, BODE and GOLD were included in the evaluation of the cohort.

4.3.5. Subject Characteristics 2008 - 2009

Table 4.11 illustrates the demographics of the cohort at this timeframe. The cohort in 2008-2009 comprises 50 % of females with a mean age of 70.0 ± 9.3 . In terms of smoking status, 58% were current smokers and 25.3 % were ex-smokers whereas only 16.7% were non-smokers. The mean pack year history was 30.9 ± 19.4 . The subjects were slightly overweight with a mean BMI of 27.0 ± 5.7 and demonstrated moderate severity in terms of spirometry with a mean FEV₁% predicted of 56.4 ± 22.2 , with a mean MRC dyspnoea score of 3.20 ± 1.4 out of 5, median BOD score was 3 (range 0-7) and BODE index scores of 2.77 ± 2.0 . The GOLD severity score was 2.36 ± 0.9 .

Age (years)		70.0±9.3
Gender (m/f)	Male	49 (50.0%)
	Female	49 (50.0%)
Smoking Status	Current	55 (58.0%)
	Exsmoker	24 (25.3%)
	Non smoker	19 (16.7%)
Pack years (years)		30.9±19.4
BMI (kg/m ²)		27.0±5.7
FEV ₁ (L)		1.40±0.6
FEV ₁ % predicted		56.4±22.2
MRC (1-5)		3.20±1.4
6MWT (n=73)		294.0± 100.0
GOLD (1-4)		2.36±0.9
Median BOD Scores (Range)		3.00(0-7)
Median BOD categories (Range)		2.00 (1-4)
BODE Scores (1-10)		4.13±3.0
BODE Quartiles (1-4)		1.96±0.9

Table 4.11. Demographic Characteristics of the Cohort 2008 -2009 (n=98). BOD scores and categories are presented as median and range.

The mean scores in GOLD, MRC, FEV₁% predicted, BOD and BODE indicate that the cohort have a range of disease symptoms from mild and moderate to severe.

Figures 4.27-4.31 shows the score distribution of BOD, GOLD and BODE scores of severity in the study cohort. More than 50% of the cohort had a BOD score of 3 or less, BOD categories of 2 or less and a GOLD score of 2 or less. As in the previous time frames, the three severity indices, BOD, GOLD and BODE, indicate different degrees of severity in the same cohort.

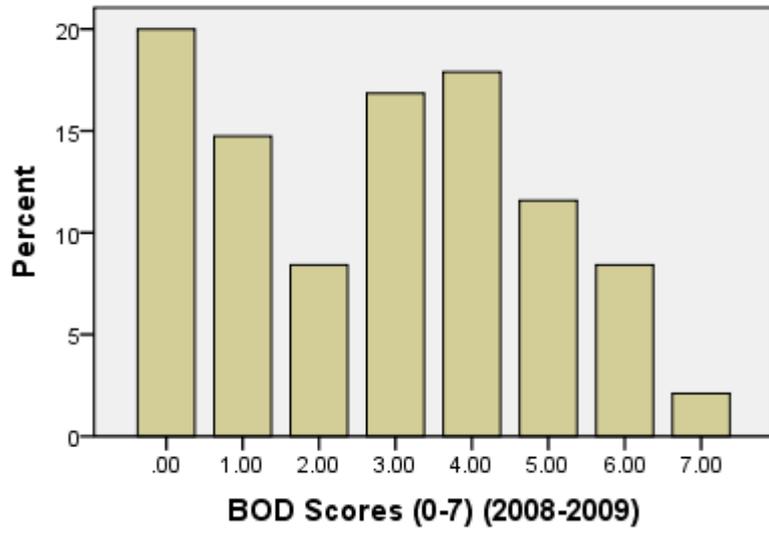


Figure 4.27. BOD score distribution (2008-2009)

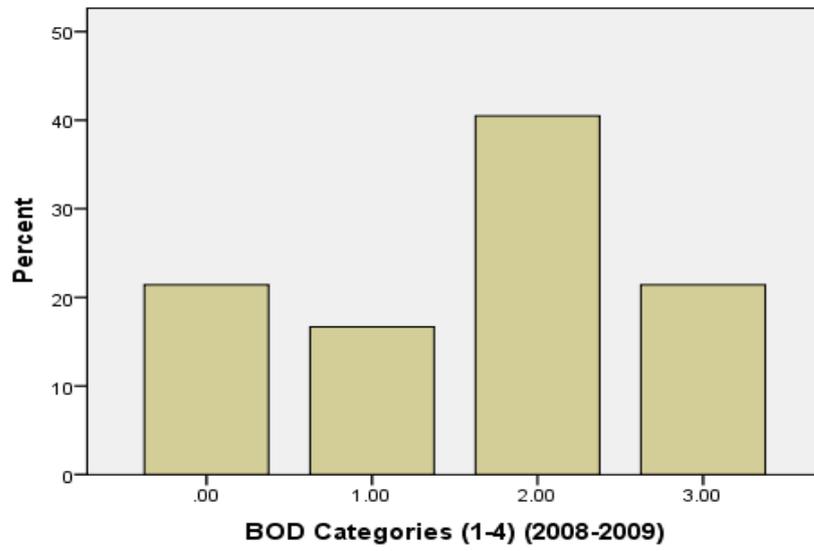


Figure 4.28. BOD categories distribution (2008-2009)

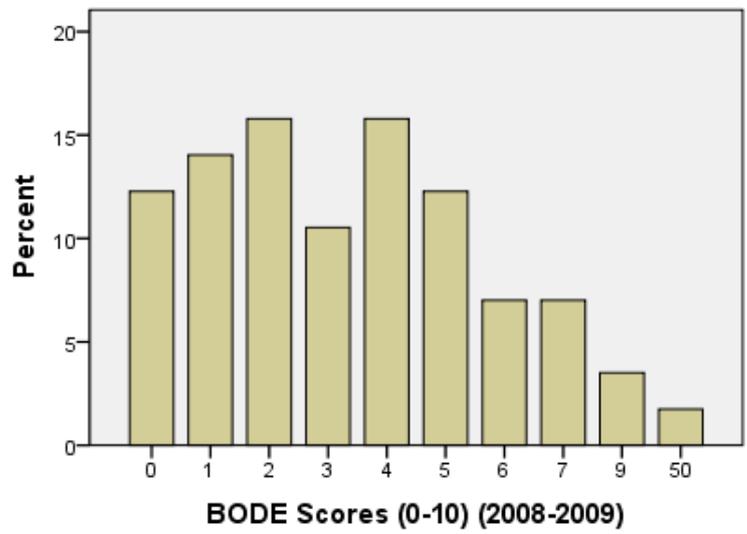


Figure 4.29. BODE score distribution (2008-2009)

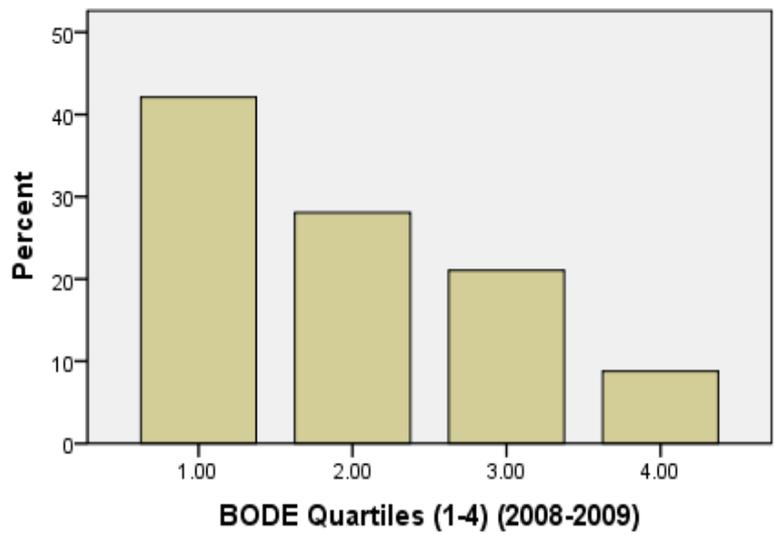


Figure 4.30. BODE Quartiles distribution (2008-2009)

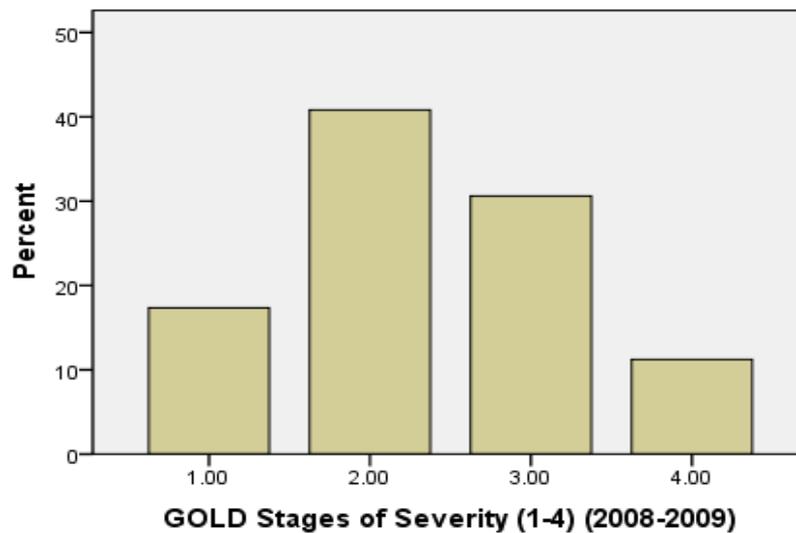


Figure 4.31. GOLD stages of severity distribution (2008-2009)

Table 4.12 shows the progression of the different indices of COPD (BOD, BODE, FEV₁% predicted and GOLD) and demonstrates that all of the measurements deteriorated over time. However, out of these only BOD (median value) and FEV₁% predicted (absolute value) changed significantly showing their sensitivity to change over time in this cohort.

n=98	2007-2008	2008-2009	P value
Median BOD Score (Range)	2.00 (0-7)	3.00 (0-7)	0.009
BODE Score (n=56)	3.05 ± 2.2	4.15 ± 6.7	ns
Median BOD Categories (Range)	2.00 (1-4)	2.00 (1-4)	0.04
BODE Quartiles (n=56)	1.78 ± 0.9	1.96 ± 1.0	ns
FEV₁ % Predicted	59.0 ± 22.8	56.4 ± 22.2	0.02
GOLD Score	2.31 ± 0.9	2.35 ± 0.9	ns

Table 4.12. Progression of the Indices over time (12 months interval). The BOD data are presented in median and range.

The covariates known to influence COPD outcomes were recorded in the 2007/8 cohort including the number of exacerbations in the last 12 months, comorbidity scores and other indices of severity such as BOD, BODE and GOLD. The comorbidity scores are the scores obtained from the cohort in 2007/8 for other coexisting diseases the patients have, as detailed in chapter 3 with the help of Charlson comorbidity index. These were compared between survivors and deceased subjects during the 2007-2010 timeframe (table 4.13). There is a significant differences were found between survivors and those who died within the next 12 months of the study in terms of their measured BOD scores, BOD categories (median value), GOLD stages and frequency of exacerbation. But frequency of exacerbations was less in the deceased group than in survivors measured in the 2007-2008 cohort. This seems to indicate that the mean number of exacerbations (which were less than 1/year) does not influence the death rate in this cohort of the present study. Similarly, comorbidity scores as measured by Charlson index of severity (explained in Methodology Section in detail) and BODE (scores and quartiles) were not statistically significant between the two groups.

	Survivors (n=98)	Deceased (n=15)	P value
Age	69.0±9.1	74.3±9.9	0.009
Pack years	33.3±20.1	40.4±21.4	<0.001
Charlson Index	3.7±1.6	3.0±1.7	ns
FEV₁% Predicted	60.8±22.5	44.7±18.7	0.003
Exacerbation frequency	0.5±0.9	0.1±0.4	0.04
GOLD	2.21±0.8	2.95±0.8	<0.001
Median BOD Scores (Range)	2 (0-7)	5 (0-7)	<0.001
Median BOD Categories (Range)	2(1-4)	3(1-4)	<0.001
BODE Scores	3.26±2.3	2.30±1.5	ns
BODE Quartiles	1.94±1.0	1.33±0.6	ns

Table 4.13. BOD, BODE, GOLD & FEV₁ % as measured at 2007/8 and 2008/9 in Survivors and Deceased Members of the Cohort. BOD data are presented as median and range.

The KM survival curves were not computed for 2008/9 interval because of fewer deaths in the members of the cohort whose BOD (n=3) and BODE (n=1) were recorded during the second phase of the study.

The author also tried to explore the variation in BOD over this 12 month period and its relationship to the relative risk of death however only 4 deaths were observed and therefore no conclusions were made. However, it is noticeable that 3 out of 4 (who died) had worse BOD scores than at baseline.

4.4 Discussion

There are a variety of factors that are known to influence the prognosis and the natural history of COPD (Dolan et al., 2005; CDC, 2008). Some of these factors have been incorporated in the severity indices (GOLD, BOD, and BODE) and have been evaluated in this study in a cohort of 458 patients.

The present study is somewhat unique as compared to other relevant studies in three aspects. First, the cohort of this study comprises 49% of females whereas in most other similar studies the proportion of females were less than this. Ko and colleagues (2011) who assessed the variation in the BODE index over three years had only 14% of females in their cohort. Similarly another study by Esteban and co-workers (2010 and 2011) that compared predictive capacity of multidimensional indices had only 3.9 and 2.3% of females in their two cohorts. A study to investigate the predictive ability of the multidimensional index BODE for anxious and depressive patients with COPD had 20% of females (Li et al., 2010). Moreover, the BODE study itself had only 8% females. One study which had similar proportion of females (50%) in their cohort to the current one was carried out to examine the gender difference in the distribution of BODE index (de Torres et al., 2007). The reason for a higher proportion of females in this study compared with other international cohorts may be due to a higher prevalence of smoking among women in the UK. The relatively high proportion of females does not reflect the clinical experience in the UK (Soriano et al., 2000; British Lung Foundation, 2005), as it is well established that primary care physicians tend to prefer a

diagnosis other than COPD in women when presented with a clinical scenario typical of COPD (Chapman et al., 2001). Nonetheless, the higher proportion of females in this study as compared to most of the other studies provides the opportunity, for health care professionals, to apply the study findings to both genders.

The second uniqueness of this study is the degree of severity as measured by spirometry. The present study cohort mainly consists of patients with a mild to moderate degree of lung function decline ($60.9 \pm 20.0\%$) in contrast to other similar studies where the mean FEV₁% predicted were 43.0 ± 19.0 (Celli et al., 2004) 51.0 ± 22.0 (Ko et al., 2011); 55.0 ± 13.3 (Esteban et al., 2010); 49.7 ± 14.6 (Esteban et al., 2011); and 45.2 ± 16.2 and 52.4 ± 16.2 in the two cohorts (Puhan et al., 2009). Additionally Li and co-workers (2010) who evaluated the predictive ability of BODE in depressive patients had a mean FEV₁% of 42.5 ± 10.8 to 46.2 ± 11.0 in their cohort. The lesser degree of severity in this study therefore has been helpful in assessing the progression of the disease over a 10 year period. The reason is probably that patients for this study were recruited from primary care clinics whereas the others mentioned mainly consisted of hospital clinic patients (Ko et al., 2011; Puhan et al., 2009; Celli et al., 2004), who are likely to have been admitted with a more severe condition.

The last and perhaps the most significant difference of this study is its duration. There have been very few studies (Medalion et al., 2004; Van-Domburg et al., 2002; Leavitt et al., 2006) that have examined the mortality as an outcome in patients with mild to moderate form of disease (at baseline) over a 10 year period. For this reason, the findings of this study may attract the attention of healthcare professionals considering the longstanding nature of COPD.

The results show that BOD and GOLD are different from one another in a COPD cohort over a 10 year period. Furthermore, when KMSA and ROC were performed between GOLD and Survival years and then BOD and Survival years, it was shown that BOD was more effective than GOLD in predicting 10 years' mortality in patients with COPD. Similarly, when KMSA curves were computed to analyse three years survival, BOD was again more effective than GOLD. However, few deaths occurred during three years (2007-2010). The results show that BOD is a better predictor of mortality in years than GOLD and BODE. A recent study (Ko et al., 2011) suggests that serial changes in BODE were not significant when the 12th, 18th and

24th months indices were compared. This may be because baseline BODE index was measured in patients within 6-8 weeks after recovery from acute exacerbation of COPD.

The results of Cox regression analysis also suggest that BOD index is more accurate as a prognostic indicator than GOLD stages when confounders such as pack years and age were taken into account (Tables 4.4 and 4.5). Additionally, the ROC curve (figure 4.11) clearly indicates that BOD works more effectively than GOLD to predict COPD mortality. The areas under the curve (AUC) for BOD and GOLD were 0.64 and 0.58 and p values were <0.001 and 0.01 respectively. In other words, neither was very good as the p-value merely gives an indication of how much faith to place in the coefficient. However, when the ROC curves were obtained for 3 years mortality data in the time 2 databases, the AUC improved significantly for both BOD and GOLD (0.73 and 0.71 respectively).

Similarly when different indices of severity were compared over a 12 month period to assess variation in their respective scores, both median BOD scores and BOD categories were significantly changed over time (p=0.006 and 0.04) suggesting that the BOD index is more sensitive to change than BODE or GOLD. The only other measurement that changed significantly over time was FEV₁ % predicted (p=0.02) suggesting the role of lung functions in disease progression.

Furthermore, when the indices were compared between deceased and survived members of the cohort (between 2007-2010), the results suggest that BOD as well as GOLD stages of severity scores are significantly higher in the deceased group. The most surprising fact is that in the deceased group the BODE scores were little better or lower (p>0.05) than in the survived group. The reason may be that the number of patients was lower than in the assessment of BOD and GOLD as very few patients were able to perform the six minute walk test (a major component of the BODE Index). This inability to exercise emphasizes the need for an index without an exercise test which could be applied to a larger group of patients. Another reason for a lower number of patients with measured BODE scores was that some patients were not willing to attend hospital and were recruited by visiting their homes. The exercise could therefore not be performed. However, BOD scores were easily obtained in these patients.

While predicting risk of mortality may benefit health care professionals in their management of a patient with COPD, opportunity for survival is more likely to appeal to the patients themselves. An observational study (Cote et al., 2005) has shown that completion of a pulmonary rehabilitation programme improved BODE scores and was associated with prediction of increased survival. In the present study, individuals with severe and very severe impairment of FEV₁ (GOLD III and IV) were found to be long-term survivors. That is, they had around 60 % chance of survival for 10 years or more (Figure 4.8). On the other hand, individuals with the worst category of BOD scores (6-7) showed only around 42% probability of survival for 10 years or more (Figure 4.7). When the data were adjusted for potential covariates including age and pack years that are known to influence mortality in these patients (Esteban et al., 2008; Reilly et al., 2008; Shavelle et al., 2009), both the BOD index and GOLD stages of severity improved their predictive power (figure 4.9 and 4.10). This reflects the sensitivity and predictive power of the BOD index in patients with COPD. Demonstrating prognosis to individual patients may promote smoking cessation, and encourage a healthy diet and compliance with a programme of pulmonary rehabilitation, interventions that are required to improve a BOD score and by inference survival (Cote et al., 2005).

Overall, the results suggest that BOD is a better predictor of progression of disease than GOLD. This emphasizes the multisystemic nature of the disease that not only effects lung functions but also produces functional impairment (measured by MRC dyspnoea score) and body mass (measured by BMI), and both of these are components of the new BOD index.

The BOD index could be utilized to monitor progression of patients, with COPD because BOD is a simple tool for evaluation of the clinical impact of COPD. BOD performs effectively with patients seen in primary care where resources to conduct a walk test are not available and/or in those patients who are not able or not willing to perform the six minute walk test in a clinical setting due to breathlessness or any other comorbid conditions. Its value may also be in helping patients realise their prognosis.

The present study suggests that the BOD index is very simple to calculate and requires no additional resources except spirometry e.g. equipment, trained staff, space, patient's consent and time. Because of this it is readily applicable outside the hospital setting, in primary care facilities for example, and in developing economies. It yields multidimensional information on

each individual that relates to prognosis and therefore facilitates the planning of interventional therapies, including pulmonary rehabilitation. BOD can also be used to inform patients of their COPD risk factors, so motivating them to alter their lifestyle accordingly. However, a much larger epidemiological study is needed to attach prognostic information to individual BOD scores and make this tool simpler to use and easier to explain to patients. Additionally, further studies will be needed that assess serial BOD indices to assess its variation in patients at regular intervals.

The present study would appear to be the first longitudinal study that examines the correlation of BOD with COPD outcome by comparing 10 year, 3 year and one year mortality data in patients with COPD and the results are interestingly in its favour. Health care professionals should utilize the BOD index in their clinical settings to evaluate patients' progress and advise patients accordingly to improve their health. The index can also be utilized to motivate patients to modify their lifestyle and also to discuss the end of life care issues (Seamark et al., 2007; Goodridge, 2007) in these patients.

However, more studies are needed to explore the factors that influence motivation and mood of these patients to follow instructions from their health care provider to improve health status and wellbeing.

4.5. Conclusion

This study demonstrates that BOD which is easy to apply in all primary care settings is an effective predictor of survival. The results also suggest that BOD index is sensitive to changes significantly over time than other indices of severity and is more efficient in discriminating such as FEV₁% predicted, GOLD, and BODE.

However, further markers need to be investigated that could enhance the predictive power of BOD. These better characterise the full clinical picture of COPD, which may lead to improved understanding of disease development and as well as development of novel assessment indices of severity to monitor disease progression. In turn that may further enhance the effectiveness

of current therapies and management protocol and make it possible to treat COPD patients on an individual basis depending upon the progression of the disease.

Therefore, in the next chapter of this report (chapter 5); BOD improved by the addition of other potential indicators of COPD severity and progression has been investigated.



**AN INVESTIGATION INTO OTHER PHYSICAL MEASURES THAT
COULD BE USED TO IMPROVE UPON BOD AS A MEANS OF
PREDICTING COPD OUTCOMES**

5.1. Introduction

The previous chapter has shown that BOD can be used to predict COPD outcomes; however it may be possible to improve upon the BOD index by the inclusion of other physical measures known to impact upon COPD progression.

This chapter examines a range of potential indicators including FEV₁, BMI, MRC dyspnoea index, age, smoking history, smoking status, gender and the exercise test that could be used as measures of COPD progression. It also investigates whether their inclusion in the BOD index might improve its ability to predict COPD outcomes.

The measures investigated are:

- | | | |
|-----------|--|-----------------------------------|
| a. | Demographics and other non-specific Indicators | (Personal Marker) |
| b. | Body Composition (Fat Free Mass & Fat Mass) | (Physiological Marker) |
| c. | Hand Grip Strength | (Physiological Marker) |
| d. | St. George's Respiratory Questionnaire (SGRQ) | (Health Status Marker) |
| e. | Duration of Symptoms | (Subjective/Symptomatic Marker) |
| f. | C Reactive Protein (CRP) | (Biomarker/Haematological Marker) |
| g. | Historical Height Measurement | (Physical Marker) |

5.2. Methods

The detailed methodology for the listed indicators and exclusion and inclusion criteria are explained in the Methodology section in detail (section 3.4.).

Full details of the cohort can be found in chapter 3.

5.2.1. Data Analysis

The database used to analyse the different indicators of disease progression in this chapter is different depending upon the number of times that data were recorded. For example SGRQ scores were obtained twice during the study phase, one year apart, whereas CRP was recorded just once. Similarly, height and MRC dyspnoea score were recorded thrice whereas hand grip strength and lean body mass were recorded only twice, 12 months apart. The lists of variables and number of times these were recorded are presented in table 5.1.

When measurements were only recorded once or twice and when the sample size is small because of a high dropout rate (including reducing in numbers due to subjects dying) it was not possible to draw firm conclusions. However, within these constraints, analysis below attempts to explore the relationship of COPD outcomes in terms of mortality, number of years of survival and health status with the measures investigated.

Measurements recorded once	Measurements recorded twice	Measurements recorded three times	Measurements derived from recorded data
Charlson Index	No of Exacerbations	Age	Lean to fat ratio Fat mass
Comorbidities	Lean body mass	Height	Percent predicted hand grip strength
Survived and deceased	Hand grip strength	Smoking status Pack years	Symptoms duration at baseline
Survival time in years	SGRQ Scores		BODE
CRP	Symptoms Duration		GOLD

Table 5.1. Additional potential indicators of COPD progression and the number of times the measurements were recorded in this study.

5.3. RESULTS

5.3.1. Baseline characteristics

Altogether 161 patients were recruited for this analysis. Table 5.2 represents the overall characteristics of study participant at baseline and at follow-ups in 2007/8 and 2008/9.

n=161	Male N=77	Female N=84	Test for Normality	p value
Age	70.7±8.8	69.2±9.8	par	ns
Pack years	30.2±22.8	32.6±19.9	npar	ns
No of Exacerbations	0.55±0.88	0.52±0.90	npar	ns
Charlson Index	3.92±1.8	3.34±1.5	par	ns
MRC Dyspnoea Score (2007-2008)	2.96±1.2	3.17±1.3	par	ns
MRC Dyspnoea Score (2008-2009)	3.30±1.4	3.15±1.4	par	ns
SMWT (n=92) (2007-2008)	288.6±85.0	261.1±93.5	par	<0.001
SMWT (n=92) (2007-2008)	317.5±86.7	282.4±87.7	par	<0.001
Lean Body Mass (2007-2008)	55.2±10.2	40.3±10.3	par	<0.001
Lean Body Mass (2008-2009)	55.0±10.5	38.9±9.2	par	<0.001
Fat Mass (2007-2008)	25.7±8.7	28.8±11.2	par	ns
Fat Mass (2008-2009)	27.3±8.8	29.3±9.6	par	ns
Lean Fat Ratio (2007-2008)	2.4±0.7	1.5±0.6	par	0.009
Lean Fat Ratio (2008-2009)	2.1±0.5	1.6±1.3	par	0.02
Grip Strength (% Pred) (2007-2008)	77.5±20.4	78.5±25.1	npar	ns
Grip Strength (% Pred) (2008-2009)	76.2±21.6	74.5±24.1	npar	ns
SGRQ Symptoms Score (2007-2008)	56.9±17.6	56.3±20.5	par	ns
SGRQ Symptoms Score (2008-2009)	53.0±17.3	48.3±19.7	par	ns
SGRQ Activity Score (2007-2008)	61.7±24.0	64.9±25.1	par	ns
SGRQ Activity Score(2008-2009)	62.7±22.8	64.3±25.2	par	ns
SGRQ Impact Score(2007-2008)	35.0±17.1	34.5±21.9	npar	ns
SGRQ Impact Score(2008-2009)	33.0±18.0	27.9±18.9	npar	ns
SGRQ Total Score(2007-2008)	46.7±17.6	47.5±20.5	par	ns
SGRQ Total Score(2008-2009)	45.7±17.3	42.3±19.7	par	ns

par=parametric test; npar: non parametric test

Table 5.2. Demographics of COPD male and female subjects at baseline and in 2007/8 and 2008/9.

5.3.2. Assessment of Potential Predictors of COPD Outcomes in the 1999-2002, 2007-2008 and 2008-2009 Cohorts

The analyses below, which are based on Pearson and Spearman rank correlation (dependent on the data distribution), present the association of potential indicators recorded/measured in this study with a range of different COPD outcomes including mortality, number of years survived and HRQL (table 5.3).

Outcomes	Predictors (1999-2002)	Predictors (2007-2008)	Predictors (2008-2009)			
Mortality	Age	<0.001	Age	0.004	BMI	0.02
	BMI	0.01	BMI	0.006	SMWT	0.04
	Smoking status	0.02	Smoking status	<0.001		
	Pack years	0.001	Pack years	<0.001		
	MRC	<0.001	MRC	0.003		
	% Predicted FEV₁	<0.001	% Predicted FEV₁	...0.001		
	GOLD	0.003	GOLD	<0.001		
	BOD Score	<0.001	BOD	<0.001		
BOD categories	<0.001					
No of years survived	Age	<0.001	Age	<0.006	Smoking status	<0.001
	BMI	0.001	BMI	0.01	Pack years	0.05
	Pack years	0.002	Pack years	0.002	MRC	0.01
	MRC	<0.001	MRC	0.004	SMWT	0.04
	% Predicted FEV₁	<0.001	% Predicted FEV₁	0.001	Fat mass	0.01
	GOLD	<0.001	GOLD	<0.001		
	BOD Score	<0.001	BOD score	<0.001		
	BOD categories	<0.001	BOD categories	<0.001		
SGRQ (%) Scores (HRQL)			Age	0.03	BMI	0.02
			Pack years	0.002	MRC	<0.001
			Handgrip Strength	0.01	Comorbidity Index	0.02
			MRC	<0.001	SMWT	0.001
			Comorbidity Index	0.02	Past exacerbation	0.008
			SMWT	<0.001	Handgrip	0.01
			Past exacerbation	0.008	% PredictedFEV₁	<0.001
			% Predicted FEV₁	<0.001	GOLD	0.001
			GOLD	0.001	BOD score	< 0.001
			BOD score	< 0.001	BOD categories	< 0.001
			BOD categories	< 0.001	BODE	0.002
			BODE	< 0.001	BODE Quartiles	< 0.001
			BODE Quartiles	< 0.001		

Table 5.3. Indicators of COPD and the statistical significance of comparison with multiple measures of outcomes (Red colour texts indicate negative correlations).

(a) MORTALITY AND NUMBER OF YEARS SURVIVED

Table 5.3 represents the relationship of additional potential indicators of severity and COPD outcomes such as mortality, number of years survived and health status. Only those variables that showed statistical significance ($p < 0.05$) are presented in this table. These variables are discussed below.

(i) Age

The results show that age is significantly correlated with mortality ($p = < 0.001$ and 0.004) thus a higher age is associated with a higher probability of death in the 1999-2002 and 2007-2008 cohort. However, in the 2008-2009 cohort age did not show any significant correlation with mortality in these patients.

Age is also significantly but negatively correlated with number of years survived in 1999-2002 cohort and positively correlated in 2007-2008 cohort ($p < 0.001$ and 0.006).

(ii) BMI

The results show that BMI is significantly correlated with mortality and indicates that a lower BMI is associated with a higher probability of death in all members of the cohort ($p = < 0.01$, 0.006 and 0.02 respectively) at all the time frames.

BMI is also negatively correlated with number of years survived, and this correlation was found both in the 1999-2002 and 2007-2008 cohorts ($p = 0.001$ and 0.01).

(iii) Smoking

The results show patients who were exsmokers were significantly correlated with higher mortality as indicated in 1999-2002 and 2007-2008 cohorts ($p = < 0.02$, < 0.001). However, in the 2008-2009 cohort smoking status, either current or exsmoking did not show any significant correlation with mortality in these patients. Furthermore, in terms of pack year history, a higher

number of pack years was associated with a higher mortality in 1999-2002 and 2007-2008 cohorts ($p=0.001$ and <0.001).

Pack year history was also significantly correlated with number of year survived ($p=0.002$, 0.002 and 0.005) at all times.

(iv) MRC Dyspnoea Score

The results show that the MRC Score is significantly correlated with mortality ($p = <0.001$ and 0.003) and indicates that a higher MRC is associated with a higher probability of death in both the 1999-2002 and 2007-2008 cohorts. However, in the 2008-2009 cohort, there was no meaningful correlation with mortality in patients with COPD and MRC score.

The analysis also shows that the MRC dyspnoea score was significantly and negatively correlated with number of years survived in patients with COPD. ($p < 0.001$, 0.004 and 0.01) indicating the high MRC score associated with less number of years survived.

(v) Lung Function

FEV₁ % predicted and GOLD stages of severity also show significant correlation with mortality in both 1999-2002 and 2007-2008 cohorts. However FEV₁ % predicted indicates negative correlation with mortality.

In other words, lower % predicted FEV₁ associated with higher mortality in both cohorts ($p < 0.001$ and 0.001). Similarly, higher GOLD stages of severity was also associated with higher mortality in both cohorts ($p = 0.003$ and < 0.001).

On the other hand, both FEV₁ % predicted ($p < 0.001$ and 0.001) and higher GOLD stages of severity ($p = < 0.001$ and < 0.001) were associated with higher number of years survived.

(vi) Six Minute Walk Test (SMWT)

The SMWT only significantly correlated with mortality and number of years survived in 2008-2009 cohort ($p < 0.04$).

(vii) Multidimensional Indices of Severity

The results related to multidimensional index BOD scores and categories are already presented in chapter 4.

(b) HEALTH RELATED QUALITY OF LIFE (ASSESSED BY SGRQ)

Most of the potential indicators which are correlated with mortality and number of years survived are also associated with health status measurements as assessed by SGRQ. The indicators that are positively and significantly correlated with health related quality of life include age ($p = 0.03$), pack years ($p = 0.03$), MRC ($p < 0.001$), comorbidity ($p = 0.02$), GOLD ($p < 0.001$) and number of past exacerbations ($p = 0.008$) in 2007-2008 cohort. In contrast, only comorbidity index ($p = 0.02$), number of past exacerbations ($p = 0.008$) and GOLD ($p < 0.001$) found significant in the 2008-2009 cohort.

Some indicators were negatively but significantly correlated with SGRQ score in both 2007-8 and 2008-9 cohorts. These include hand grip strength ($p = 0.01$ and 0.01), SMWT ($p < 0.001$ and < 0.001), and FEV₁ % predicted ($p < 0.001$ and < 0.001). However, there were some additional variables which become significantly associated with HRQL in the 2008-2009 cohort. These include BMI ($p = 0.02$) and MRC ($p = 0.001$).

The multidimensional indices BOD and BODE (scores, categories, quartiles) were all positively and significantly correlated ($p < 0.001$) with both BOD and BODE ($p = 0.002$ for both indices) scores in 2007-2008 and 2008-2009 cohorts.

Table 5.3 summarizes the significant correlations of all the indicators and indices in all three cohorts of this study. The most noticeable point is that lean body mass, fat mass, symptoms duration and CRP did not show any significant relationship with any of the COPD outcome variables.

5.3.3. Indicators that could potentially be used to improve upon the BOD Index

From the correlation coefficients three indicators were significantly associated with mortality in patients with COPD. These include the personal indicator age and the habitual indicators smoking status (smoker, ex-smokers and non-smokers) and pack years of smoking. Backward linear regression analysis was carried out to identify factors that influence BOD index. In table 5.4 below it is shown that age and pack years were among the most significant predictors of BOD scores in patients with COPD ($p < 0.05$ and 0.001 respectively).

Dependant variables	Unstandardized Coefficients	Standardized Coefficients	Sig.	95.0% Confidence Interval for B	
	B	Beta		Lower Bound	Upper Bound
1 (Constant)	.465		.347	-.505	1.436
Age(years) (1999-2002)	.015	.092	.054	.000	.029
Pack years (1999-2002)	.013	.157	.002	.005	.021
Smoking status (1999-2002)	-.023	-.010	.836	-.240	.194
2 (Constant)	.448		.357	-.508	1.405
Age(years) (1999-2002)	.014	.091	.055	.000	.029
Pack years (1999-2002)	.013	.154	.001	.005	.020

Table 5.4. Linear Regression analysis. Dependent Variable: BOD Scores (0-7) (1999-2002)

Therefore, it was decided to incorporate these two factors into the BOD index and to examine whether or not the BOD scores then were better able to predict outcomes.

5.3.4.

BOD PLUS

This section will evaluate potential indicators that can be incorporated into the BOD index to improve the ability of the index to predict COPD outcomes including mortality, number of years survived and health related quality of life as measured by SGRQ scores.

1. Mortality and Number of years Survived

In order to incorporate pack years and age into the BOD index, it is essential to score these new potential indicators so that data analysis can be carried out. For this reason the scores are given to age and pack years. For age, the scores are given as recommended by a recently carried out study (Puhan et al., 2009) which categorized age into 6 categories (0-5).

On the other hand, there is no consensus on how to categorize pack year history in patients with COPD and previous studies (Furberg et al., 2005; Vestbo et al., 2008; Shavelle et al., 2009) have used different categorisation for their data some of which appeared opportunistic. For example Mannino and co-workers (2003) divided their cohort into three categories i.e. <30, 30-59 and ≥ 60 pack years. Another study classified pack years into never, 1-25, 25-50 and >50 pack years (Fred et al.; 1998). Similarly Folsom and colleagues (1998) divided pack years as 1-19; 20-39 and ≥ 40 years. Additionally the influence of pack years on COPD outcomes varies between genders (Prescott et al., 1997) as well as subjects (Saccone et al., 2010). However, Hersh and colleagues (2004) stratified their COPD cohort by the categories of the number of pack-years of smoking to examine their predictability. They found that lifetime cigarette consumption [per 10 pack-years] was a significant predictor of mortality. Thus literature suggests that no standard recommendations are available that can be utilized to classify/quantify data on the basis of pack years history. Therefore, in the present study pack years history has been divided into four categories (0-10, 11-30, 31-45 and >45).

In the present study three possible indices were developed with the addition of pack year history (S) into BOD (BODS); addition of age (A) into BOD (BODA) and with the addition of both age (A) and pack years (S) into BOD (BODAS). The new indices with their respective scores are presented in table (5.5).

Indices of Severity	Measurements Used in different Models				
	BMI (kg/m ²)	FEV ₁ % (%)	MRC Score (1-5)	Age (years)	Pack years (years)
BOD Scores (0-7)	(B)	(O)	(D)	(A)	(S)
0	>21	≥65	1-2	NA	NA
1	≤21	50-64	3	NA	NA
2	NA	36-49	4	NA	NA
3	NA	≤35	5	NA	NA
BODS Scores (0-10)	(B)	(O)	(D)	(A)	(S)
0	>21	≥65	1-2	NA	0-10
1	≤21	50-64	3	NA	11-30
2	NA	36-49	4	NA	31-45
3	NA	≤35	5	NA	>45
BODA Scores (0-12)	(B)	(O)	(D)	(A)	(S)
0	>21	≥65	1-2	40-49	NA
1	≤21	50-64	3	50-59	NA
2	NA	36-49	4	60-69	NA
3	NA	≤35	5	70-79	NA
4	NA	NA	NA	≥ 80	NA
BODAS Scores (0-14)	(B)	(O)	(D)	(A)	(S)
0	>21	≥65	1-2	40-49	0-10
1	≤21	50-64	3	50-59	11-30
2	NA	36-49	4	60-69	31-45
3	NA	≤35	5	70-79	>45
4	NA	NA	NA	80-89	NA

Table 5.5. Scores of each variable used in the newly developed indices.

(a) Evaluation of Multidimensional Indices of Severity BODS, BODA and BODAS in the 1999-2002 Cohort

In order to assess new predictors that can be incorporated in the BOD index as a predictor of mortality, KMSA curves (previously explained in chapter 3 and 4 in detail) were used to show the probability of survival.

Figures 5.1 to 5.6 represent the probability of 10 years of survival in this study cohort according to their scores and categories of their respective indices. These include BODS, BODA and BODAS indices of severity.

All of these indices show a clear differentiation of the cohort between lower and higher scores according to their probability of survival over time ($p < 0.001$).

Figures 5.1 and 5.2 show BODS scores and categories and their probability of survival. The figures indicate that members of the cohort with BODS scores 7 or more out of 10 (category 3 or 4 of 4) have the lowest survival probability over time (<50%) compared to those with lower scores, in whom the probability of survival over time was more than 80%.

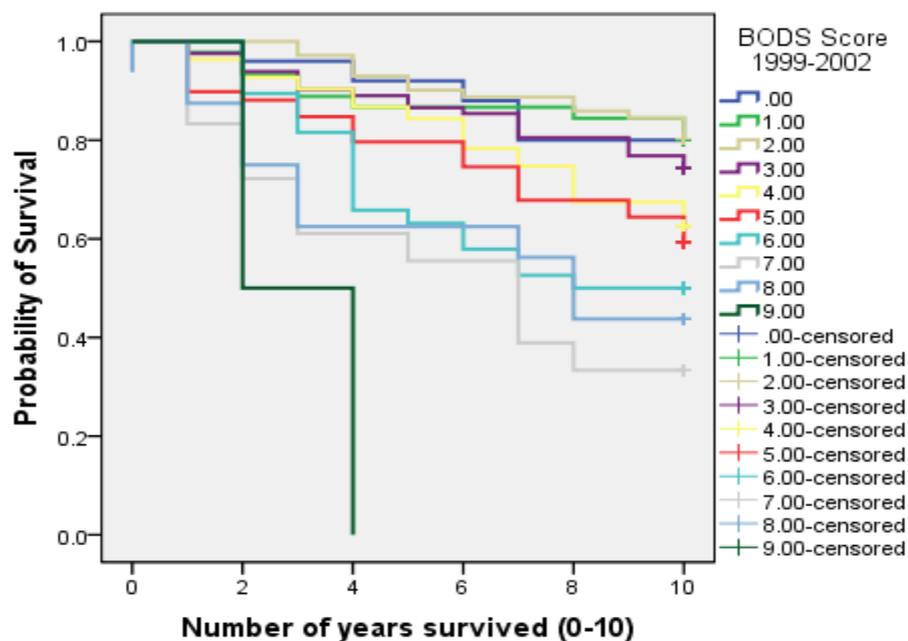


Figure 5.1. Kaplan Meier Curve using individual BODS Scores (1999-2002)

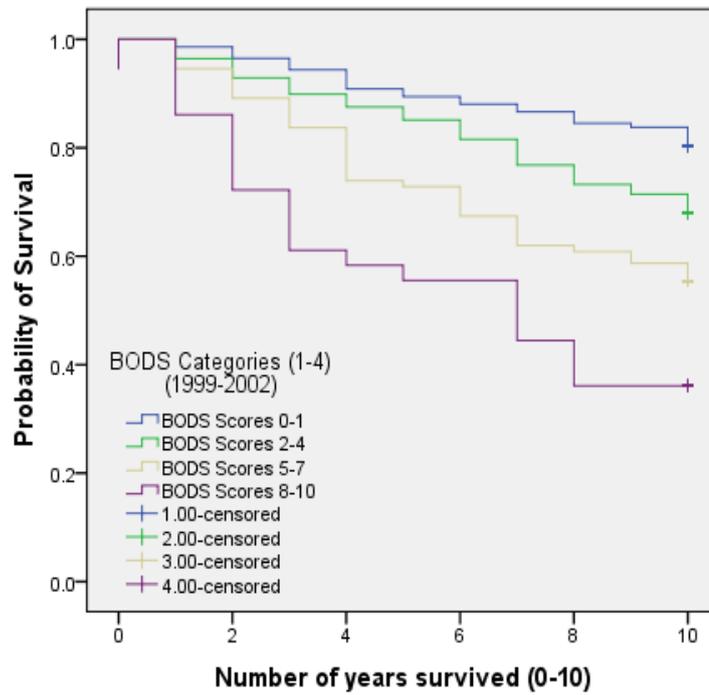


Figure 5.2. Kaplan Meier Curve using BODS categories (1999-2002)

Figures 5.3 and 5.4 show BODA scores and categories and their chances of survival. The figures indicate that members of the cohort with BODA scores 7 or more out of 12 (categories 3 or 4 out of 4) have lowest survival probability over time (<40%) compared to those with lower scores of 0, 1, 2 or 3 (categories 1 or 2 of 4), in whom the probability of survival over time was more than 80%.

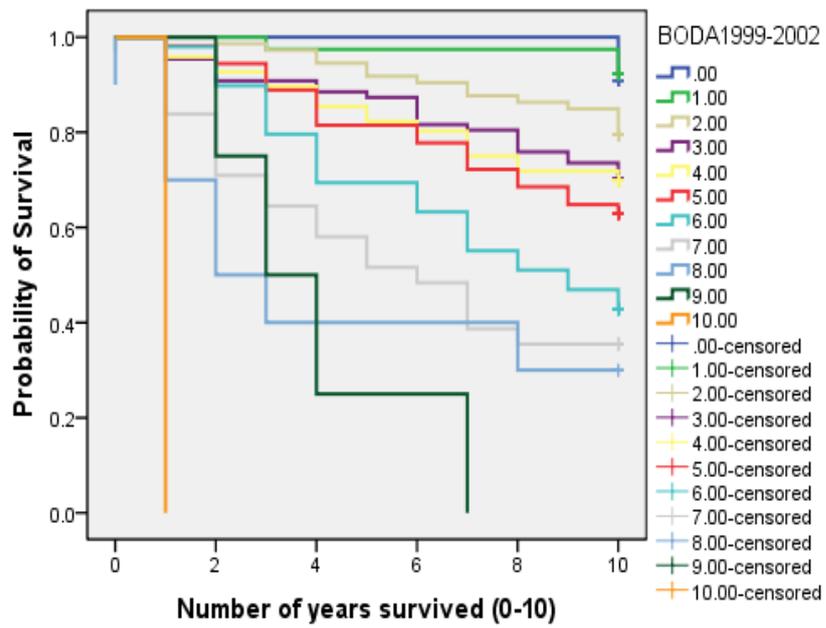


Figure 5.3. Kaplan Meier Curve using BODA scores (1999-2002)

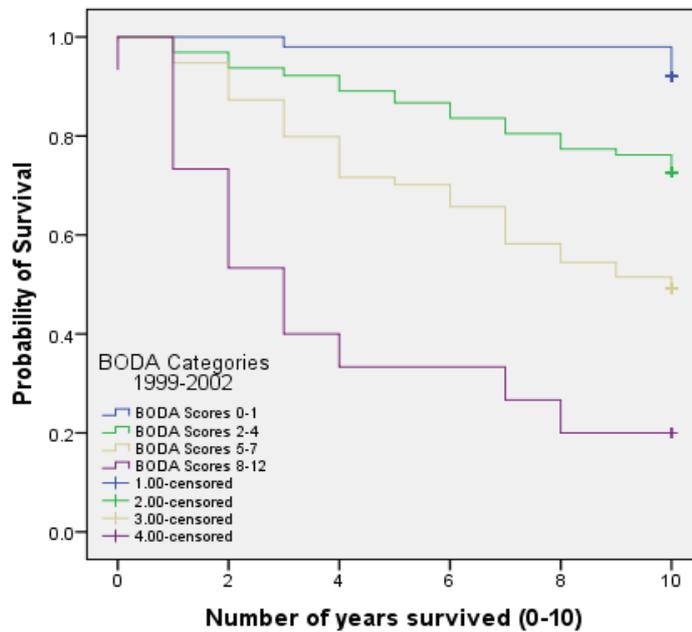


Figure 5.4. Kaplan Meier Curve using BODA categories (1999-2002)

Similarly figures 5.5 and 5.6 show BODAS scores and categories and their chances of survival. The figures indicate that members of the cohort with BODAS scores 9 or more out of 14 (category 4) have lower survival probability over time (<40%) compared to those with lower

scores of 0, 1, 2, 3 or 4 (categories 1 and 2 of 4), in whom the probability of survival over time was more than 80%.

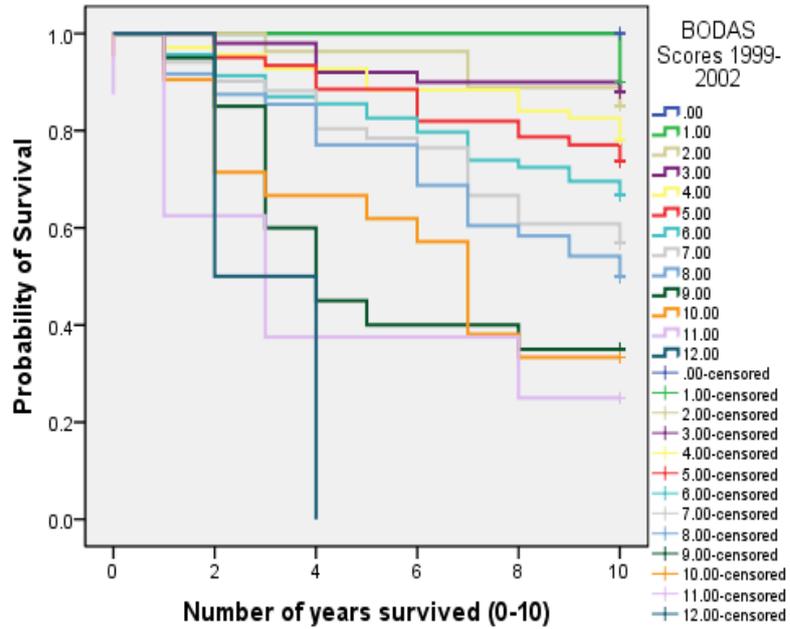


Figure 5.5. Kaplan Meier Curve using BODAS scores (1999-2002)

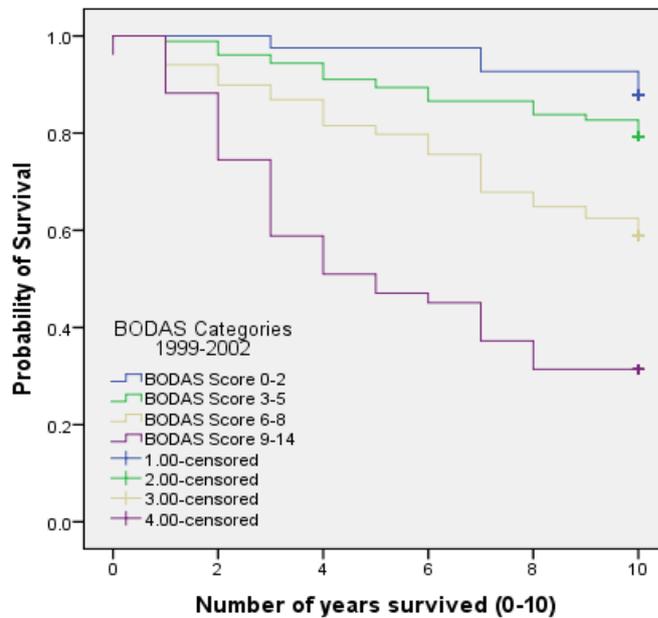


Figure 5.6. Kaplan Meier Curve using BODAS categories (1999-2002)

To explore the data further, ROC curves were used to compare the capacity of these new potential indices in predicting health outcome. The curves produced using BODS, BODA and BODAS can be found in Figure 5.7 and Table 5.6. The figure and table clearly indicate that BODAS has the highest ROC value for predicting mortality in the cohort. The areas under the curve (AUC) for BODAS, BODA, BODS and BOD were 0.72, 0.70., 0.66 and 0.63 respectively ($p < 0.0001$ for all indices). Thus the addition of age and smoking history to BOD provides an important development and this is clearly demonstrated in the K-M analysis for individual BODAS scores and categories (Figures 5.5 & 5.6). BODAS is therefore a highly appropriate candidate for generalised use when exercise capacity of COPD patients cannot be undertaken.

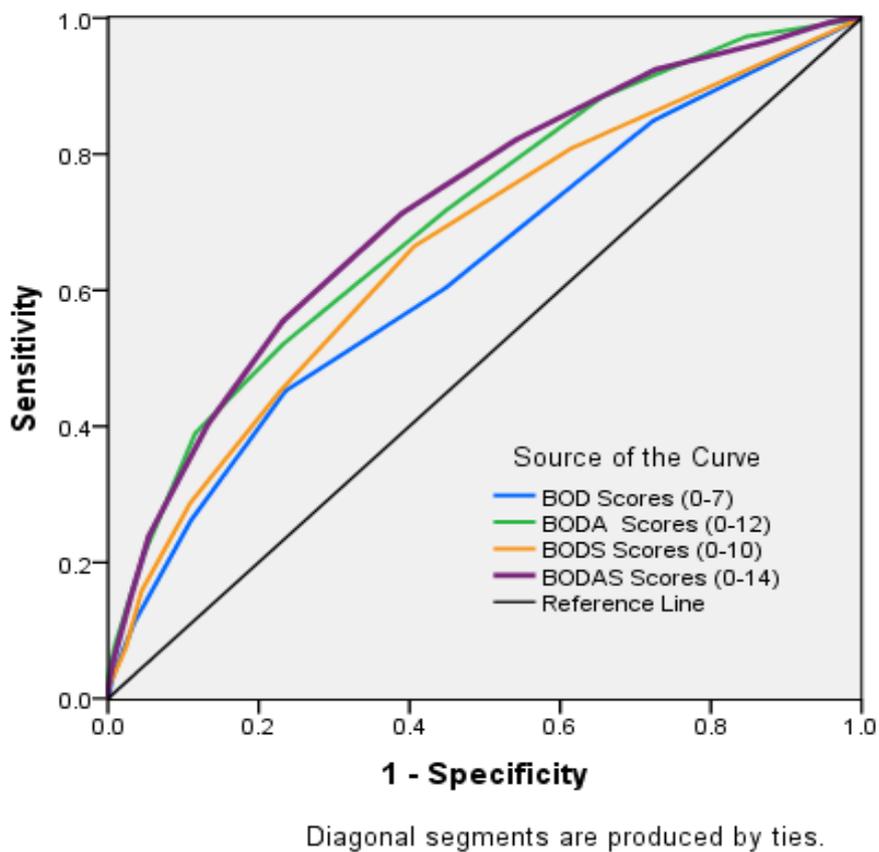


Figure 5.7. ROC Curve shows sensitivity and 1-specificity between indices (1999-2002)

Multidimensional Indices of Severity 1999-2002	Area under the Curve (AUC)	Std. Error	p value	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
BOD Scores (0-7)	.629	.029	<0.0001	.573	.685
BODS Scores (0-10)	.663	.028	<0.0001	.608	.717
BODA Scores (0-12)	.708	.026	<0.0001	.657	.759
BODAS Scores (0-14)	.721	.026	<0.0001	.671	.772

Table 5.6. ROC for different indices of COPD severity with 10 years Mortality

(b) Validation of the multidimensional indices of severity BODS, BODA and BODAS in the 2007-2008 surviving cohort

KMSA curves have also been plotted in order to assess BODS, BODA and BODAS indices of severity as a predictor of 3 year survival (2007-2010). For this analysis, categories of each respective index score were used, as not enough deaths were observed to represent each individual score (Figures 5.8-5.11).

Figure 5.8 shows that those with a higher BOD category of 4 have only around 50 % probability of surviving more than 3 years. In contrast, patients with BOD categories of 0 and 1 have more than a 90 % probability of surviving more than 3 years.

Figure 5.9 represents BODS categories and their KMSA curve shows that subjects with higher category scores (of 4) have least chance of survival as compared to those with lower categories. However the discrimination between categories is not as clear as in the case of BOD categories.

Figure 5.10 indicates categories of BODA and their probability of survival for 3 years or more and shows that members of the cohort with higher BODA categories have less chance of 3 years survival than those with lower categories (60% vs >90%).

Similarly, figure 5.11 shows categories of BODAS index. This figure also shows that patients with BODAS categories of 4 have less survival probability of surviving for three years than those with 1 or 2 category (90% vs 70%).

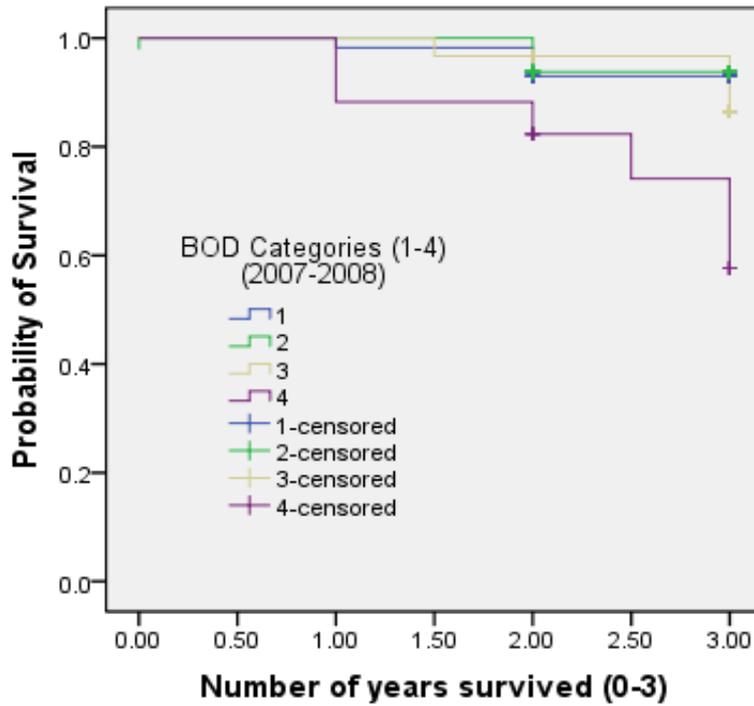


Figure 5.8. Kaplan Meier Curve using BOD categories (2007-2008)

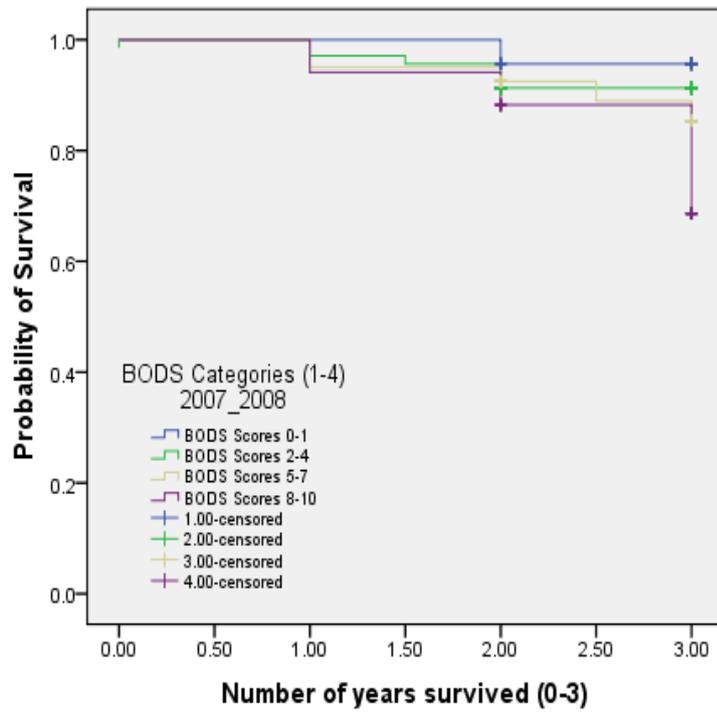


Figure 5.9. Kaplan Meier Curve using BODS categories (2007-2008)

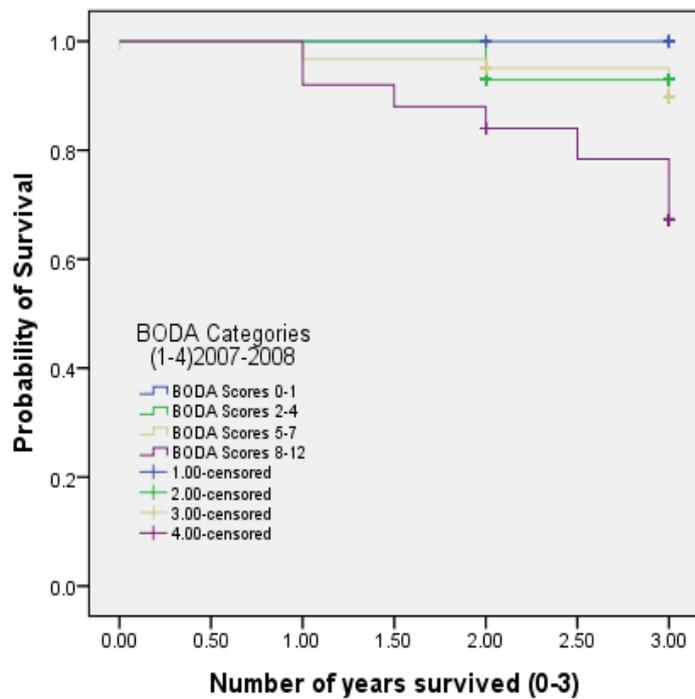


Figure 5.10. Kaplan Meier Curve using BODA Categories (2007-2008)

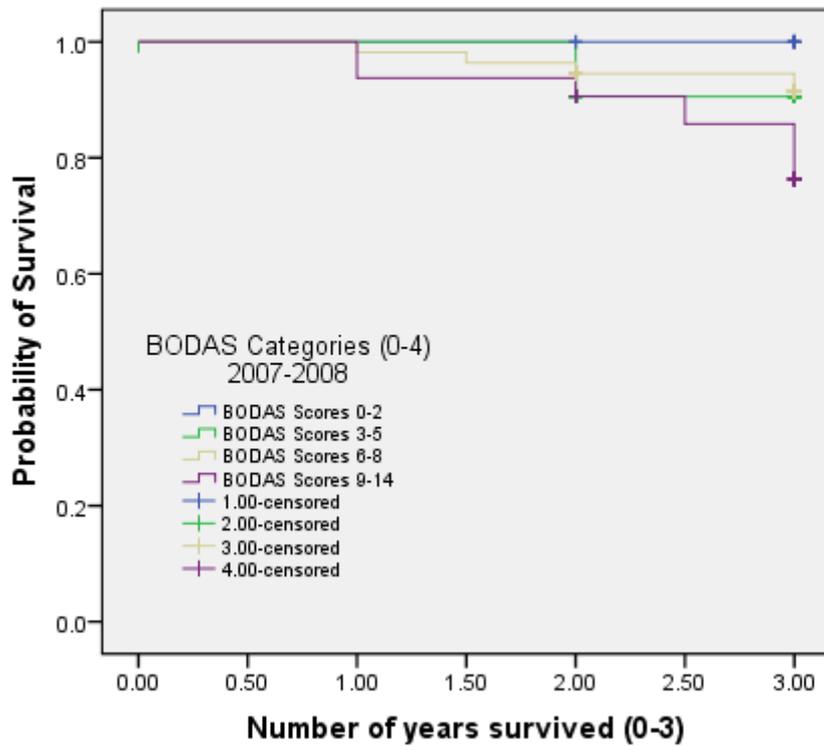
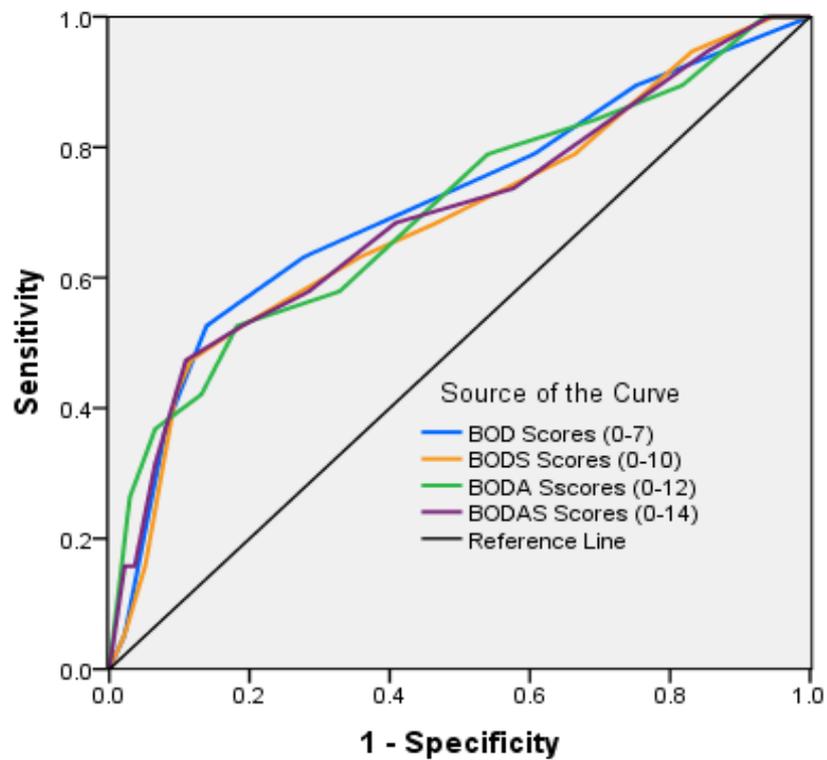


Figure 5.11. Kaplan Meier Curve using BODAS categories (2007-2008)

On further analysis, the capacity of these new potential indices in predicting health outcome was examined using ROC as shown in Figure 5.12 and Table 5.7. The figure and table indicate that BOD worked better than other indices (BODS, BODA and BODAS) in terms of predicting COPD mortality. The areas under the curve (AUC) for BOD, BODS, BODA and BODAS were 0.71, 0.68., 0.70 and 0.69 respectively (and their p values were <0.003; 0.008, 0.005, 0.006 respectively).



Diagonal segments are produced by ties.

Figure 5.12. ROC Curve shows sensitivity and 1-specificity between indices (2007-2010)

Indices of Severity 2007-2008	Area under the Curve (AUC)	Std. Error	p value	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
BOD Scores (0-7)	.711	.070	.003	.573	.848
BODS Scores (0-10)	.688	.071	.008	.549	.827
BODA Scores (0-12)	.700	.071	.005	.561	.839
BODAS Scores (0-14)	.696	.072	.006	.555	.836

Table 5.7. ROC for different indices of COPD severity with 3 years mortality

The indices were not assessed either by KM survival curves or ROC curves because of the fewer deaths in the members of the cohort for whom BOD, BODS, BODA and BODAS scores were calculated. (n=3).

2. HEALTH RELATED QUALITY OF LIFE (ASSESSED BY SGRQ)

Most of the potential indicators that are correlated with mortality and number of years survived were also assessed for their association with health status as an outcome. All the indices (BOD, BODS, BODA, and BODAS) are similarly significantly correlated with health related quality of life (see appendix for results).

The data of SGRQ Scores were then divided into two categories on the basis of cut-off values of 0-49 vs 50 to 100. The chi-square test indicates that lower categories of indices have better health status and higher categories have worst SGRQ scores in all the indices ($p < 0.001$) as shown in figures 5.13, 5.15, 5.17, 5.19 for all potential COPD indices.

The univariate analysis shows that the mean scores of SGRQ are significantly different between individual scores of all the indices of severity ($p < 0.001$) as shown in figures 5.14, 5.16, 5.18, 5.20 for each potential COPD indices.

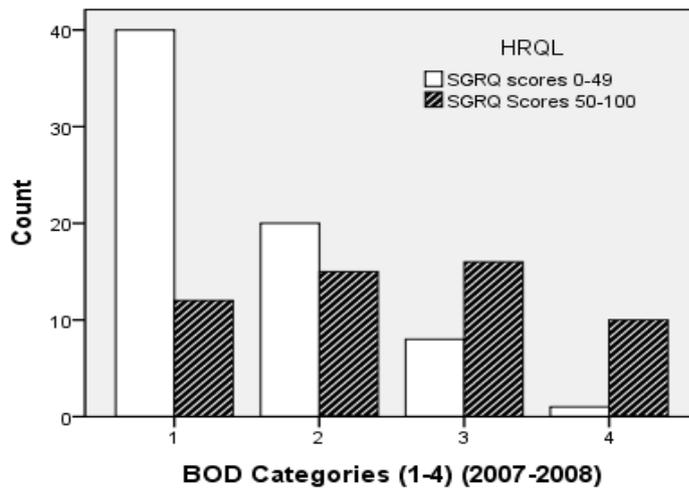


Figure 5.13. BOD categories and SGRQ Score categories

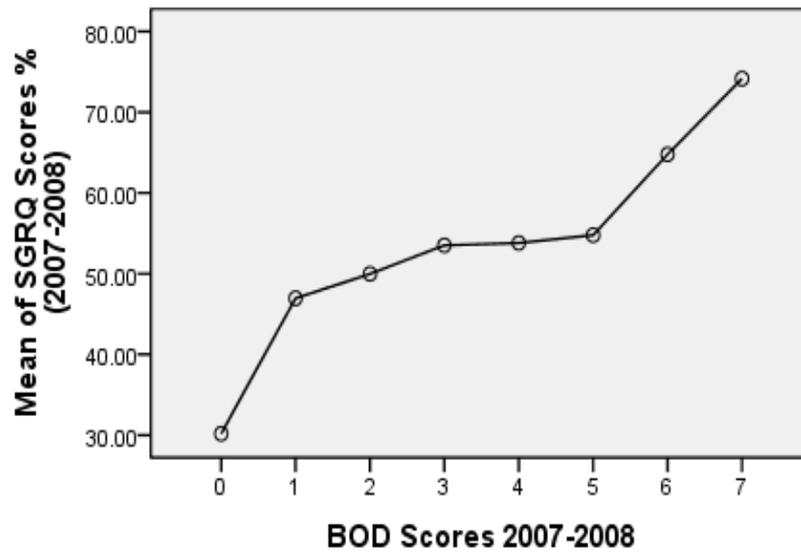


Figure 5.14. The relationship between BOD Scores and Mean SGRQ scores

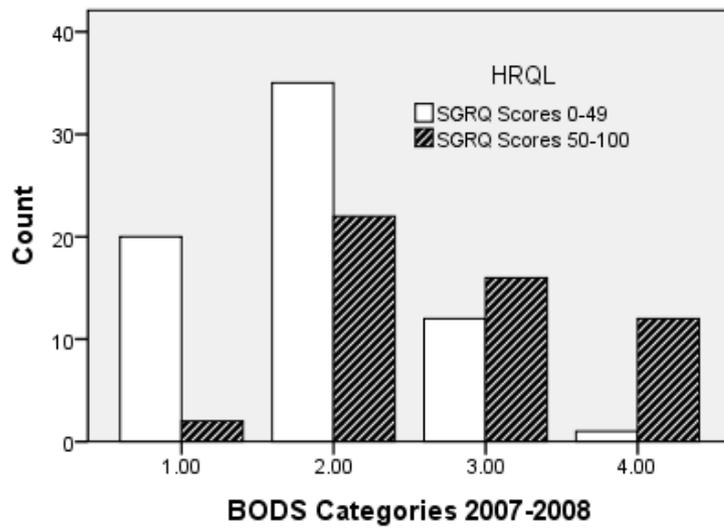


Figure 5.15. BODS categories and SGRQ Score categories

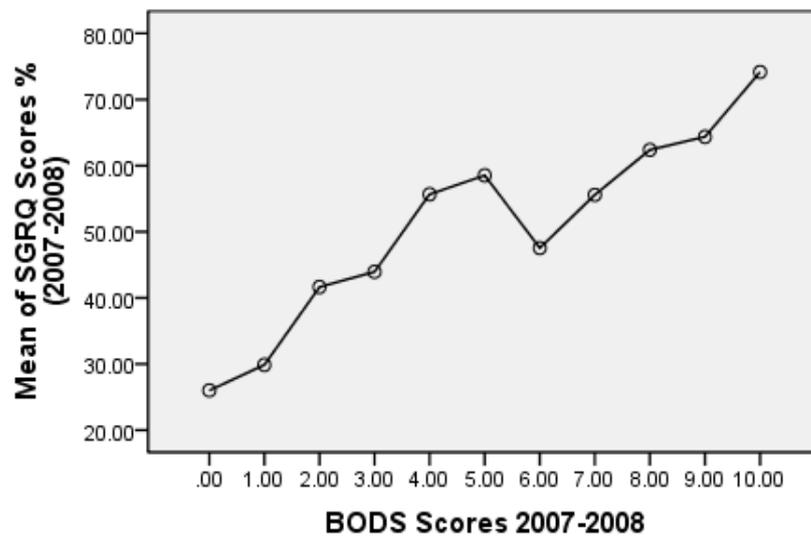


Figure 5.16. The relationship between BODS Scores and Mean SGRQ scores

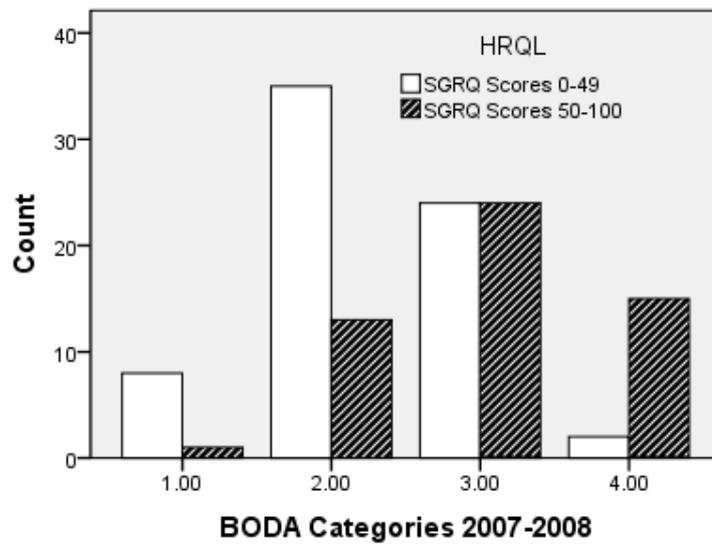


Figure 5.17. BODA categories and SGRQ Score categories

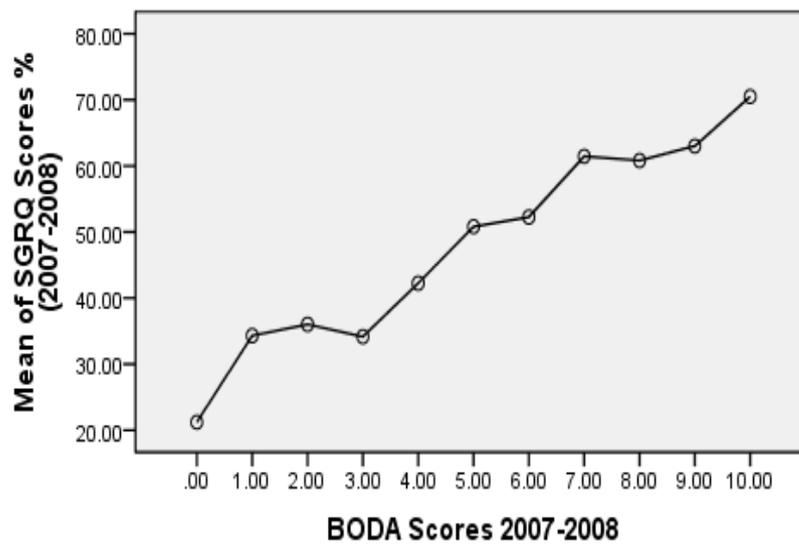


Figure 5.18. The relationship between BODA Scores and Mean SGRQ scores

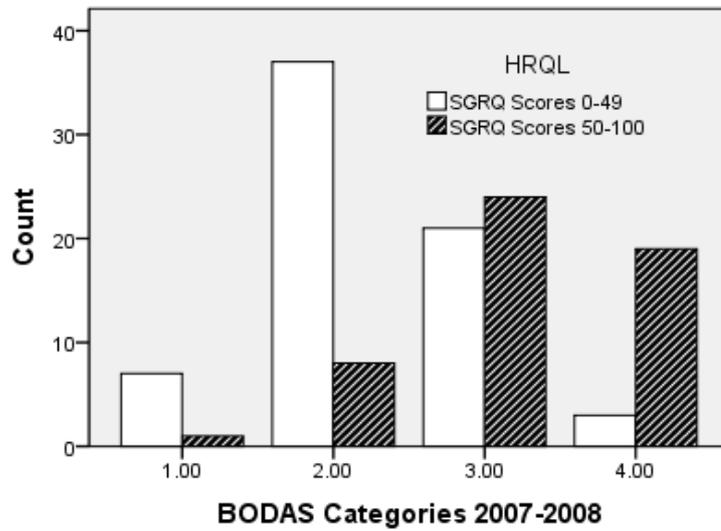


Figure 5.19. BODAS categories and SGRQ Score categories

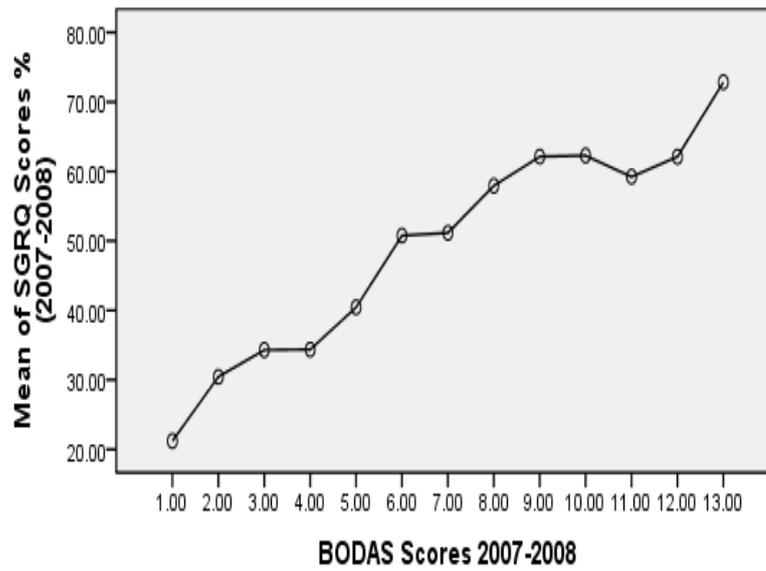


Figure 5.20. The relationship between BODAS Scores and Mean SGRQ scores

5.4. Discussion

5.4.1. Introduction

This chapter has explored potential measures that could be used to improve upon BOD as a prognostic indicator. Its relationship with other COPD outcomes such as mortality, number of years survived and health related quality of life has been explored to reflect the clinical impact of the disease.

5.4.2. Potential Measures

The potential measures that were assessed in this study were age, smoking status and smoking history, gender, FEV₁ % predicted, comorbidities, number of past exacerbations, SMWT, MRC dyspnoea score, body mass index, body composition, lean body mass, handgrip strength, health status, CRP, duration of symptoms and historical height.

Many studies have examined the role of age in COPD outcomes (Britton et al., 2003; Puhan et al., 2009); however, no firm conclusion can be made on the basis of their findings. But, age adjustment should always be considered in clinical research involving patients with COPD because of its relationship with mortality (Britton et al., 2003; Puhan et al., 2009). COPD is more prevalent in people > 45 years and is highest in elderly patients over the age of 65 (Hurd, 2000, Sullivan et al., 2000). The present study supports previous findings in terms of the age of COPD sufferers (mean age 69.5 ± 8.7 and 64.5 ± 9.4 in COPD) - presented in table 5.1. Further analysis in the present study supports the finding of Puhan and co-workers who developed the ADO index (Puhan et al, 2009) consisting of Age, MRC Dyspnoea Score and Airway obstruction scores works better than a “recalibrated” BODE index in predicting mortality in patients with COPD and underlines the effect of age on 3 year mortality in patients with COPD. When age was added as a covariate in the BOD model, however, ROC analysis was shown that BOD becomes more sensitive indicator of mortality when age added to the index (Figure 5.12 and Table 5.7). This suggests that consideration should always be given to age when exploring mortality in COPD and other COPD outcomes in these patients.

Tobacco smoke is a very well known risk factor in the development, progression, comorbidity and mortality of COPD and present research also shows a high prevalence of both current and exsmokers and a high pack-year history in this cohort.

The present study supports previous findings (Fletcher et al., 1976; Zaher et al., 2004) that both ex-smoking and current smoking influenced disease progression and mortality. This is shown in table 5.3 where pack years of smoking significantly correlated with COPD outcomes including the BOD index (Table 5.4).

The ROC curve improves the BOD index when the years of smoking was added in the BOD index. The above findings suggest that the assessment of the smoking status of COPD patients is important especially in relation to exacerbation frequency as shown with the DOSE index (Jones et al.; 2010). This suggests that smoking cessation intervention methods should be promptly discussed with the patient by the primary care physician and that smoking in COPD is an issue that may be vital for patients. It also suggests that larger scale research is needed in order to explore the impact of smoking cessation on prognosis in COPD. The data in this study are related to the burden of smoking and not to when individual subjects stopped smoking.

Traditionally, COPD has been associated with the male gender; however, in the last decade COPD has become an increasing problem among women in UK (Soriano et al., 2000) and has been recently shown in the Spanish population (Torres et al., 2010). In the present study the number of female subjects was marginally higher than males (51% vs 49%) in contrast to other studies where the levels are 14% vs 86% in Japan (Ko et al., 2010) and 4% vs 96% in Spain (Esteban et al., 2010). Hypothetically, this changing trend of COPD is simply because smoking rates are now becoming higher or at least equal in women compared to men. This is indicated by the demographical findings of the present study results where the pack-year history is 30.2 ± 22.8 in men vs 32.6 ± 19.9 in women. Similarly, 52% of females were current smokers in our cohort in contrast to 44% of males. Furthermore, in the analysis of BOD with mortality, the KMSA shows that BOD had the same effect in females as males, when gender specific analyses were performed. However, our findings could not be compared with other similar studies due to higher number of males in those studies. Thus it is very difficult to make the judgement that gender itself has a great impact on mortality as the study did not have the power to detect ($p=0.07$). As one of the potentially most important factors, it should always be

considered when researchers examine COPD outcomes and more research should be carried out to further explore any gender related difference in COPD outcomes.

COPD patients have a higher prevalence of co-morbidities than other chronic diseases. A previous study by Ferrer and colleagues (1997) reported 84% of patients with one or more co-morbidities. Another study, which compared comorbidities in COPD and controls, reported 73% prevalence of one or more co-morbidities in COPD and 63% in controls (Sprenkle et al., 2004) but this difference is statistically important. In the present study, 55% of the COPD group had comorbidities at baseline which later rose to 79% in the 2008-2009 demonstrating the consequences of COPD disease over time underlining their possible impact on COPD outcomes. In the present study the mean score of the Charlson Index score was 3.8 but this did not correlate significantly with mortality. It has been also suggested that co-morbidity is an important determinant of health status in patients with COPD, independent of FEV₁ (Oostenbrink et al., 2004; van Manen et al., 2001) and of health service utilisation (Oostenbrink et al., 2004). The present study supports previous findings that comorbidities are significantly associated with health status as shown in table 5.3. But the use of Charlson index only in 2008/9 may be a confounder here.

Soler-Cataluna and colleagues (2005) were the first who were able to demonstrate that the frequency of exacerbation influenced mortality. Their study contained 304 men with COPD in Spain over 5 years and they suggested that “patients with 3 or more exacerbations had a survival rate of 30% at 5 years whereas those without exacerbation had a survival rate of 80%. Survival rate was also influenced by the need for readmission. Those requiring readmission had a 20% survival at 5 years” (Soler-Cataluna et al., 2005). The current study has recorded the frequency of exacerbations over one year from 2007/8 to 2008/9 in a group of survivors. However, too few deaths were observed during that period to reveal meaningful results.

The six minute walk test (SMWT) is frequently employed for the assessment of COPD patients, due to its high prognostic value in terms of disability, mortality, and its usefulness in evaluating long-term therapeutic interventions (Celli et al., 2004, Ko et al., 2010). Furthermore, the test is simple to perform, inexpensive, reproducible and safe. However, it does require resources of time and expertise that are unlikely to be available in the primary care setting in the UK. Also, its application in elderly patients may be problematic where an arthritic

comorbidity presents. In 2007/8 cohort SMWT correlated significantly with mortality and number of survival years and health status (Table 5.3). But the drawback was that not all patients could perform a meaningful test and some were unwilling to. For example, this test requires a large area where the test can be performed and 10% of the surviving cohort was house-bound. This indicates the extent of the practical difficulties of performing this test in elderly patients with COPD in different clinical settings. On the other hand, BOD measurements can be taken anywhere. However, the variation of SMWT in study subjects at 12 months intervals was significant ($p < 0.001$ in both genders) which shows its sensitivity over time in patients with COPD.

BMI in BOD is a surrogate for lean body mass (LBM) because loss of muscle mass has been regarded as an important indicator of the systemic manifestations of COPD (Troosters et al., 2005). In the present study, the bioelectrical impedance analysis of body composition did not yield any significant results in the 2007/8 cohort. Therefore, more longitudinal research will be needed to investigate further LBM's role in COPD outcomes.

Hand grip strength is potentially a physical indicator of disability (Rantanen et al., 1999). Therefore results of this study demonstrate significant deterioration over time both in males and females (Table 5.2). Hand grip strength also shows significant correlation with health status assessed by SGRQ scores (table 5.3) consistent with the findings of Ansari and co-workers (2007; 2012). As a consequence, the findings support hand grip strength as an important factor influencing physical impairment and thus can be used as a measure of disability in patients with COPD and also to assess health status in these patients. However more research will be needed to explore relationships with COPD related outcomes.

Many studies have found that the health status measurement is closely related to other markers of COPD outcomes such as severity, functional status and mortality. Few studies have examined health status and COPD markers over time (Lin et al., 2009; Habraken et al., 2011). In the present study, most of the SGRQ domains did not significantly change over 12 months (Table 5.2) except the impact domain of the SGRQ which slightly improved clinically and statistically ($p < 0.05$). This improvement in health status may be due to only less severely affected patients attending follow up visits and also because of the new therapies that are claimed to be effective in improving health status in these patients (Brusasco et al., 2003).

However in the present study, the medication history was not taken into account during the analysis.

The present work has examined the relationship of health status of COPD patients and multidimensional indices (BOD, BODS, BODA, and BODAS). The results of the present study provide a very comprehensive account of the relationships of SGRQ measurement with other markers of COPD severity, disability and progression. The most importantly repeated measurements of COPD related markers and health status over time adds validity to this study results and also to the validity and importance of health status measurements with SGRQ.

The data support the conclusion that measurement of health status by the SGRQ may be more useful as a prognostic tool than generic questionnaires in an elderly population with a range of severity of COPD. The study results also suggest the potential ability of multidimensional indices as a marker of health status in patients with COPD. However, more longitudinal studies with larger cohorts will be needed to validate and support the present study findings.

Many studies in the past suggested the importance of a CRP and its prognostic value in COPD severity and other outcomes (Gan et al., 2004, Dahl et al., 2007). However, the present work did not discover any relationship between CRP levels and other COPD outcomes apart from its higher value ($>3\text{mg/dl}$) in those with $\text{FEV}_1 > 60\%$ predicted which may indicate CRP's role in these patients as suggested by recent study (Stockley, 2009). Stockley's study (2009) also demonstrated that the increased level of systemic C-reactive protein was related with poorer health status and comorbid conditions such as cardiovascular disease, cancer and skeletal muscle dysfunction.

The data of the present study also show that many of the potential indicators of COPD progression and severity are significantly correlated with COPD outcomes including mortality, number of years survived and health related quality of life. However there is a lack of consistency in some of the indicators. For example, smoking status and pack years were only observed at baseline and in the follow-up cohort but not with the third cohort. On the other hand, BMI was consistently recorded. Similarly both clinical (GOLD and FEV_1 % predicted) and multidimensional indices (BOD, BODS, BODA and BODAS) of COPD severity were

highly correlated with mortality at baseline and the follow up cohort but not with the third cohort because of too few deaths.

The present study also shows that most of the potential indicators of COPD were significantly correlated with health related quality of life. Significant relationships of demographic data with HRQL were either found at baseline (age, pack years) or at follow-up (BMI). Comorbidity scores, six minute walk test and number of past exacerbations were highly correlated with health status scores in both cohorts. And indices of severity such as GOLD and FEV₁ % predicted and multidimensional indices (BOD and BODS) of COPD severity were also highly correlated with health status scores both at baseline and in the follow-up cohort. Additionally percent predicted hand grip strength also turned out to be a significant predictor of health status in later cohorts as was found in a previous study (Ansari et al., 2007; 2012).

Previous investigations (Celli et al., 2004, Ko et al., 2010) have tended to look at the application and relationship of their developed indices with other COPD outcomes such as their relationship with gender (Torres et al., 2007), depressive symptoms (An et al., 2010), health related quality of life (Martin et al., 2011), hospitalized patients, (Ko et al., 2011), patients enrolled in pulmonary rehabilitation programme (Cote and Celli, 2005) or patients with lung volume reduction surgery (Imfeld et al., 2006). However, the present study has made further attempts to improve the new BOD index with the help of other potential measures that could be incorporated into BOD. The potential measures that were chosen to improve BOD as a result of in depth analyses of all the known and potential indicators were age and pack years (See section 5.3.4).

5.4.3. BOD PLUS

The information needed to calculate BOD is easily obtainable without special resources and readily available in all primary care settings where these patients are mostly diagnosed and treated. In the original cohort BOD plus measures including age and smoking years seemed more effective than BOD alone in terms of their relationship with COPD outcomes such as mortality, number of years survived and health status (Figures 5.13-5.20). Overall, the findings suggest that multidimensional indices of severity are more beneficial to monitor COPD progression and severity as scores are consistently correlated with COPD outcomes. In

the 1999-2010 cohort, the data related to mortality and number of years survived BODAS worked better than the other potential indices BOD, BODS and BODA (Table 5.6). Figure (5.7) and table (5.6) clearly show that BODAS is the most powerful indicator of mortality as compared to other indices included in the analysis (BOD, BODA and BODS). The AUC for BODAS was 0.72 ($p < 0.0001$) which is almost the same as found in Celli BODE study where the AUC was 0.74 (Celli et al., 2004). But in terms of its utilisation, BODAS is far superior to BODE as all of its variables are easily measured and /or obtainable in all settings, and in all patients irrespective of their demographical representation, psychological status, or comorbid condition as compared to BODE where one of its components (E-Exercise test) requires expertise, resources, patients' motivation and absence of relevant comorbidities. Furthermore, BODAS consists of five different variables hence providing healthcare professionals with an opportunity to work on a range of indicators that can be modified (apart from the A-age). Therefore more possibilities are available for patients to take advantage of knowledge about their prognosis and become motivated to alter their lifestyle and behaviour. Encouraging patients to make efforts to improve their scores and to participate in pulmonary rehabilitation for instance would help them to improve their outcome and to achieve a better health status. There is therefore more chance of improvement than with BODE.

The findings could not be compared with other studies and no previous study has examined these potential indicators by means of an index. Therefore further investigation of longer duration and with larger cohort would be needed to support and validate this study finding. As age and pack years are routinely recorded in primary care settings, it should be possible to obtain this information with no additional staff, resources, or time required to get this information. Overall, the study suggests that the BODAS significantly influences both mortality and HRQL. The BODAS scores of an individual could possibly be utilized to motivate patients to make the necessary effort to improve their scores by life style modifications.

5.5. Conclusion

Findings suggest that there are many potential indicators that need examination in order to further enhance COPD assessment and improve the prediction of COPD outcomes.

The results also suggests that the addition of pack years smoking history scores (S) in BOD scores improves its accuracy by 4%.

However, none of indicators tested were able to provide total assurance that could lead to their incorporation into a new BOD index with the exception of pack year history.

Therefore, there is a need to explore other factors beyond conventional indicators such as patients' psychological status. This may help to improve patients' lifestyle and improve their attitude which may assist them as they battle against the negative consequences of the disease.

PSYCHOLOGICAL MARKER OF COPD PROGRESSION

6.1. Introduction

It is suggested that a patient's health related quality of life (HRQL) is vital in improving COPD outcomes (Jones et al., 2002) which may mean that an improvement in HRQL could lead to improvements in other COPD related measures. However, it is essential to understand all the factors that may be responsible for supporting and improving current health status (Daudey et al., 2010). This could be achieved by assessing the degree of psychological status and wellbeing of an individual. In the context of mental illness Manderscheid and colleagues (2010) define wellness as a separate aspect of an illness which refers to the degree of positive attitude and enthusiastic behaviour about healthy life.

It is believed that the level beneath current state of health (HRQL) is the lifestyle/behavioural level, followed by psychological, mental stress and motivational levels and the deepest of all is the spiritual being (Travis, 1970; Figure 2.9). A combination of all these levels describes overall wellness. Wellness assessment is believed to help in exploring feelings of an individual in an event or during a course of chronic disease. As a result, psychological intervention may be developed that could help to improve the overall natural and physical health of these patients. This in turn may influence COPD outcomes and may intercept or slow down the progression of COPD in these patients.

The purpose of this section of the thesis is to describe the development of a wellness assessment questionnaire and to apply this to study participants to investigate the role of wellness in patients with COPD and its relationship to clinical status and health status of the disease.

6.2. Methodology

An overview of the steps used to explore the concept of wellness and to design and validate the wellness questionnaire is given in Chapter 3 (section 3.8)

6.2.1. Steps in the Development of the Wellness Questionnaire

The aim and objectives related to this part of the study were to explore the views on the need for assessing wellness and to design an appropriate questionnaire that comprehensively reflects the wellness status of the study cohort. Therefore in the first phase, numerous examples of existing wellness questionnaires were reviewed to identify generally accepted domains, categories and most suitable questions used to assess wellness and from these a draft questionnaire (see appendix 2) was designed. Ethical approval was then gained from the Committee at Sunderland University. The three community settings (Age Concern and Breathe Easy, Sunderland and South Tyneside) were approached to seek their views about the concept of wellness and the questionnaire. Of importance were the ease of comprehension and the relevance of questions to our target population of COPD patients with mild, moderate and severe disease. Following feedback from the focus groups, together with discussion with the research team the questionnaire was modified and finalised.

Following approval by the NHS, LREC and the Sunderland University ethics committees, questionnaires were sent to COPD study participants by post, including a prepaid envelope and a covering letter, asking them to fill in the questionnaire and return it to the University of Sunderland. A consent form to confirm their voluntary participation in the study and an information sheet about how to complete the questionnaire were included together with contact details in case there were any concerns to discuss. If necessary a home visit or hospital appointment would be made at the patient's request.

6.3 Qualitative Data Analysis

To analyse focus group data, "content analysis" is employed. In order to carry out content analysis on text (transcribed from audio files/hand written notes) that is generated as a result of the focus group, the text is either coded or broken down into meaningful categories on the basis of a word, sentence or a phrase used that makes sense. Later themes can be generated on this

basis. The final stage is to examine the text using one of content analysis' basic methods: conceptual analysis or relational analysis (Bender & Ewbank, 1994). In the present study conceptual analysis (which is also known as thematic analysis) was used to analyse focus group data. The details are presented in section 3.8.3 (chapter 3).

6.4. Results

After critically analysing the literature, a questionnaire was initially derived consisting of potential themes/domains that would be appropriate to assess wellness status. Five domains were identified initially. These include Personal, Self-Responsibility, Daily Stress, Stress Management, and Physical wellness (See appendix 2). The researcher then attempted to explore in depth patients' psychological behaviour and how they perceived their health in terms of wellness and whether this directly or indirectly influences the clinical condition and overall health in these patients. As discussed above, the wellness questionnaire was developed using themes gathered from the literature search and the feedback gained from the focus groups using thematic analysis.

6.4.1. Development of the Wellness Assessment Questionnaire

a. General Characteristics

Focus groups 1, 2 and 3 were arranged at "Age concern", "Grindon Lane Primary Care Centre, Sunderland" and South Tyneside Hospital, South Shields respectively. In the first focus group, there were 8 participants, of whom 7 were females. The other details regarding focus group participants' characteristics and venues are presented in table 6.1. The participants in all focus groups were Caucasian.

The steps followed and the major outcomes of the focus group sessions are presented in table 6.2.

Characteristics	Focus group 1 (F1)	Focus group 2 (F2)	Focus group (F3)
Source	Age Concern, Sunderland	Breath Easy group, Sunderland	Breath Easy group, Sunderland
Induction Venue	Nursing Homes Hendon and Seaburn	Primary Care Centre, Sunderland	St. Gregory's RC Church, South Shields
Session Venue	Age Concern, Sunderland	Primary Care Centre, Sunderland	South Tyneside Hospital, South Shields
Number of Respondents (R)	8	6	6
Gender (m/f)	1/7	5/1	3/3
Age range	45-75	60-75	60-75
Health issues	None	COPD, Emphysema, Bronchiectasis.	COPD, Emphysema, Bronchiectasis.
Motivation of participants	Enthusiastic, highly motivated and enthusiastic.	Enthusiastic, highly motivated and actively took part in the discussion.	All were vocal, highly motivated and interested to discuss the questionnaire therefore actively took part in the discussion.

Table 6.1. Characteristics of Focus group participants and the session venues.

b. Sources of Analysis

- Audio transcripts
- Hand written notes by the Researcher
- Thematic analysis

The sources used to develop the questionnaire, number of domains and questions and the major outcomes of each step are summarised in table 6.2 a detailed account is presented in the next section.

Questionnaire	Initial Draft	First Version	Second Version	Third Version
Sources	Literature Review Research Team Meetings	Focus Group I	Focus Group II	Focus Group III
Domains Included	5	5	5	5
Questions Included	101	101	40	40
Action Taken		Removed, added and amended Questions and merged domains	Removed, added and amended Questions	No major changes made
Major Outcomes	Initial draft prepared and focus group sessions arranged	Substantial reduction in the length of the questionnaire. Identified new theme “Spirituality”	Validated first version of the questionnaire from people with respiratory problems	Preparation of the final version of the questionnaire from people with respiratory problems.

Table 6.2. Development of the Wellness Questionnaire

c. Themes Included in the Questionnaire

The results presented in this section are based on focus group participants views about assessment of wellness and potential themes that could improve the initial draft of the questionnaire.

The themes sought from the focus groups will be presented together with respondents’ transcribed data for each section.

Theme 1: Personality

In the initial draft 5 questions were included.

However, during the first focus group sessions, members were in agreement that this section should be included in the questionnaire. However, they criticized some of the questions as itemised below.

Questions about physical appearance shouldn't be asked because I don't know how to respond. (F1R7).

Another member added "I don't want to answer this question" (F1R1)

Another suggested an alternative to this question and said,

"I think what you feel inside is more important than what you feel about your physical appearance" (F1R3).

Theme 2: Self-Responsibility Related Wellness

The second domain in the initial questionnaire draft was "Self Responsibility" which consisted of 10 questions.

The only question removed from this section was "If I were to have an emergency with my car, I would be prepared"

As most members either use public transport or do not drive, it was decided to remove this question. Some of the questions were modified for clarity.

A consensus was found among focus group members and therefore no major changes were made in this domain.

Theme 3: Daily Stress

This domain initially contained 15 questions. However, the focus group discussion reduced this number by identifying stress factors that patients with respiratory problems commonly faced.

For example,

“To me, managing finances is extremely stressful, you know what I mean” (F1R8)

Several members gave reasons for the different worries about their overall health and wellbeing which may contribute to making their lives stressful.

“...question on mental wellness and stress because of housework I do believe you can add” (F2R5).

Another interesting fact that came out is that the diagnosis of COPD is also a stressing factor for patients particularly when the patient had to share this bad news with their family or relative.

A member quoted concerns of one of her colleagues that had breathing problems and said,

“I know a woman; she is not with us today. She said that when she was diagnosed she was kind of obsessed by her family because they were so worried about that” (F3R1)

Theme 4: Stress Management

This was the most common domain found in the literature in relation to wellness. However, a substantial reduction was made after the focus group discussion as the participants suggested that the section was too long and also that most of the questions were hard to answer and not appropriate to an assessment of wellness. It was also suggested that these questions should be merged into the “Daily Stress section”.

One participant said,

“It is important to be in good health but it is not the end. Or I would say there is more to being in good health than just basic mind and body care umm and to me mental, physical emotional wellbeing is also very important”. (F1R1)

“Full questions work better than statements for example the question about alcohol “I don’t drink alcohol in excess” could be rephrased as “are you tempted to drink?” (F1R4)

Theme 5: Physical Wellness

This domain of the questionnaire initially had 4 questions. However after the focus groups the questions were modified for clarity.

For example a question that asked “Are you within 20% of your ideal weight?” was felt to be very difficult to calculate and answer. Therefore the question was modified to “do you maintain a desirable weight”?

Similarly, more questions were generated as a result of the focus group views. Areas included were:

“I decided to do regular exercise to be fit and well but unfortunately my age doesn’t allow me to do so as and when I need to. However, when I heard about somebody who is trying hard and struggling to become physically fit just like me, it motivated me to do so.....”(F1R6)

Another important source of stress was found to be the weight gain which is a common problem with the elderly particularly due to inactivity, lack of exercise or comorbidity.

For example, a member stated,

“Well, my main concern is weight and I try to find ways to lose weight you know...but I feel a bit low at times because of thisyou know....is that what you may call wellness??” (F1R5).

“I am the kind of person who is a bit lax about exercise..... .mmm.....and lose my enthusiasm suddenlywell....I know it is important for my healthy lifestyle ...that you may call wellness.....you know” (F1R5).

Another said,

“.....I think wellness is reflected from what you are eating, your concerns about weightusing nutritional supplements and leisure groups of all sorts, and if not, something wrong is going on..... may be any health problem or any other stress or what I may call “Wellness disturbance” that contributes to lost interest in such activities” (F1R7)

“I use water tablets”

“I have IBS”

“I have no problem with my bowels, but I take tablets for combatting water retention, this can cause some stress, if I need to pass water and I do not have access to a toilet. My breathing is often affected. But it is usually OK after relieving myself”

Underlining the importance of other related symptoms, patients with COPD may have, that influence their disease progression.

In the present study, the research found that patients with COPD understand the role of diet in their disease progression; however, they need proper guidelines and support. One respondent comments in the section related to dietary intake and states that..

“I don’t know what is the best food that improves my breathing”

This statement shows that patients do realize that it is not only the weight that needs to be controlled but that dietary modifications may also be needed to control symptoms, disease progression and overall wellbeing in these patients. However, this area needs to be explored further.

Environment is another important theme identified during the focus group discussions. The participants clearly expressed their views on environment and its role on health.

For example, a member of the focus group stated,

“..... my body system and my belief helps me fight against germs and live in healthy clean and mmm germs free environment I would say” (F1R1)

The group members also identified potential factors that makes environment worse and put people’s health at risk and also highlighted steps that could be taken to fight against those negative consequences that are harmful to health.

“I try to maintain a good hygiene personally as well as to my surroundings..... taking shower daily, wash my hands whenever use toilets, touching doors or touching any dusty things, before eating meals and also for shaking hands with others and for a good oral hygiene, brushing my teeth and also wearing clean clothes” (F1R1).

“Clean environment is also very important.....as it helps maintaining physical health especially and prevent body interaction with the germs” (F1R5)

“I have begun a diet (3 weeks ago) in order to lose weight to help breathing. I will persevere as I realize how important it is”

d. New Theme Identified During the Focus group Session

Spirituality was a theme that emerged in the first focus group discussion. It had not initially been included in a first draft of the questionnaire as the literature did not suggest it as a potential factor to assess Wellness or health.

Theme 6. Spiritual Wellness

At the end of the first focus group session, the group was asked as if there was any other issue that could be incorporated in the questionnaire to assess wellness, three female members of the

group initiated a discussion considering spirituality as a wellness indicator and were supported by other members.

As, one member stated,

“I tend to go to church when I am well and fit and that gives me a feeling of relaxation” (F1R1)
Supported by another participant and said,

“.....yes. Lot of people feel great when they go out for worship” (F3R2).

Participants also expressed their feelings about nature. One said,

“I feel enthusiastic and enjoy every aspect of life and nature (F1R6)”

Participant also shared their views about spirituality and its role in daily life.

A member said,

“I think spirituality is like a sense of belonging to our creator and it really helps when you believe that there is a bigger power up there to help you through your problems and pains.”
(F1R2)

The comment of F1R2 was supported by another member of the group.

She said,

“I agree and spirituality and beliefs become more important when you are going through difficulties and then you want to get help from God and your beliefs get stronger and stronger, I think” (F1R7).

Some believe that spirituality helps in reducing stresses in life. In this regard one participant stated,

“I mostly try to utilize my beliefs in coping and dealing with my pain, my illness and general stresses of my life and it really helps, I feel”. (F1R8).

It was further said,

“I tend to go to church when I am well and fit and that gives me a feeling of relaxation” (F1R1).

Participants also considered faith and beliefs as a mean of coping and positive hope.

One member stated,

“...belief gives a new hope to cope with your problems.... (F1R5).

The participants also identified meditation as a source of relaxation.

For example, one participant said,

“.....to me the main solution to your mental wellbeing is meditation. I do it regularly ammm and I think it also helps in keeping you busy and mentally fit.....” (F1R6).

Meditation is a method of relaxation that helps to overcome or re-shape the physiological and psychological reactions to the illness or stress. The focus group members also discussed advantages of being a firm believer or having faith or participating in regular worship.

Finally the consensus was that spirituality was important to include.

The major themes incorporated in the final version of the questionnaire are presented in table 6.3 with the keywords used by the participants.

Wellness Related Issues/ Emergent Themes	Key words used
Personal/Physical Wellness	lack of exercise, Weight gain, what to eat, nutritional supplements, best food
Self-Responsibility Related Wellness	Germ Free environment, healthy and clean
Emotional Wellness	very angry, “I get stressed by my family, frustrated about DIY in a house, share feelings
Mental Wellness	Stress due to Family, stress due to Finance, Lack of Exercise, Age, hate drugs, body pain, and loss of interest.
Spirituality	Mediation, Church, God, Prayers, Many people go to church

Table 6.3. Themes generated for Wellness Questionnaire.

6.4.2. Views on the design of the Respiratory Wellness Questionnaire

This section presents the focus group views on other aspects of the questionnaire. These include differing dimensions of the questionnaire such as contents, wordings, length, response format, sequence of the questions and the lay out.

Initially, participants were asked to comment on the design and type of questions asked including choice of questions. The views of the participants on the questionnaire design were very clear and mostly in support. However some criticisms and suggestions were also made.

Participants responded by suggesting that the questionnaire was too long and therefore time consuming.

A member said,

“The questionnaire seemed to be too time consuming (F1R3 and all participants expressed their agreement by nodding their heads) which is supported by other members of the group as they thought that “it is most important to be addressed” (F1R2).

Participants also criticized a few questions included in the questionnaire.

As one participant said,

“ Some participants also made valuable comments on the way the questions were written”.

The participants were then asked to comment on the lay out and format of the questionnaire. The members again showed their interest and the following responses were made.

A member said,

“...questionnaire looks fine” (F1R6)

Another said,

“...questions are very good” (F1R8)

and another said,

“Excellent” (F1R3) or “...these are nice questions” (F1R1)

“Yeah, I thought were great questions.... I think the whole exercises are well laid out really. (F2R1)

The participants not only commented on the layout but also the language used.

As one member stated,

“They are pretty straight forward questions really.....” (F2R2)

Another said,

“It covers quite a wide area which is important really...” (F3R2)

Interestingly, the group members of each focus group also commented on the response format suggesting a sliding scale of 0-10 or 0-4 or Likert scale which they felt would be better than an analogue scale or a line.

A participant stated,

“For scoring, Sliding scale 0-10 would be better or a line” (F1R6)

“Different sections could be scored differently. That is on a scale of 1 to 10, 1 to 4 or other optional method to record responses...” (F1R8)

“I like those options” (F3R1)

Furthermore, when participants were asked to comment on the layout of the questionnaire a positive response was obtained..

For example,

“... fairly very well laid out generally...” (F2R3)

and

“..... Fairly straight forward.....” (F2R4)

Another said,

“.... great questions.... well laid out really” (F2R1).

A participant also stated,

“..... certainly the questionnaire is excellent and some questions where you have to say more and there are additional spaces where you can add.” (F3R5).

As noted earlier where the criticism was made by the first focus group members that the questionnaire seemed too long, the author asked the third focus group (F3) if participants thought that the questionnaire is still too long.

The following responses were made from members of focus group 3.

“No” (F3R1)

“It covers a wide range” (F3R2)

“Not really, I think” (F3R3)

A consensus was therefore derived from the focus group members suggesting the questionnaire was well designed, well-structured, easy to understand and covers a reasonable range of health and wellbeing related issues.

6.4.3. Interpretative Analysis

The preceding sections show that the focus group participants were very interested in the discussion topic. Many members of the groups expressed their views and their daily life experiences openly and in a friendly way with explanations where needed and/or requested.

Overall, participants were fully aware and understood the importance of assessing Wellness and its role in their overall health and wellbeing.

The discussions suggested that people are no longer relying on doctors or hospitals to make them better, if they get mildly sick. Instead, their approach has been changed to disease prevention by taking self-responsibility, for instance in making their environment clean and pathogen free. Additionally, they try to maintain or improve their current health status to a maximum level.

Overall, the focus group discussions were focused, composed, helpful, and results oriented. For example, the major new theme of spirituality emerged as a result of the focus group discussions; questions addressing “Spirituality” were initially not in the questionnaire. The literature (Sulmasy et al., 2006; Puchalski, 2001) also supports the role of spirituality in health outcomes in different diseases. However, no previous study has examined its role in patients with COPD. In discussing this domain, it was felt that questions asked should be capable of being answered by those with no declared faith or belief in a god as well as those in practising religion.

The first two focus groups highlighted a number of strengths, some areas for improvement, and some significant comments to be made. The third focus group helped to validate the questionnaire contents, in a very comprehensive manner, by making comments on each and every statement using the different phrases and key words presented in table 6.3.

6.4.4. Use of the Wellness Assessment Questionnaire in COPD Subjects

The names and NHS number of the subjects in the original 1999-2002 cohort were submitted to the PCT and from the registrar general data of those subjects that were deceased was obtained. The final version of the questionnaires was sent to survivors (n=134) together with a letter of invitation, patient information sheet, consent form and a postage-paid envelope for returning the completed questionnaire. Completed questionnaires were returned by only 27 subjects. A further four had died in the intervening period, 14 were returned as undeliverable and 10 sent refusals.

Qualitative analysis was carried out on the 27 questionnaires using thematic analysis based on additional comments made by study subjects relating to any aspect or section of the questionnaire. It is interesting to note that many comments were made in various sections of the questionnaire and these comments have been used to develop themes and codes and to identify and explore the psychological impact on disease outcome and the patient's clinical condition.

The baseline demographics of respondents are presented in table 6.4. It shows that the respondents have a severe clinical condition, as indicated by their FEV₁% predicted of 45.4±19.2, with a mean MRC score of 3, but with an optimal health status having a total SGRQ score of 44.1±19.6.

Baseline Demographic Characteristics of the COPD Respondents (n=27)		
Age (years)		68.8±9.3
Gender (m/f)	Male	15 (56%)
	Female	12(44%)
Pack years (years)		39.0±17.9
BMI (kg/m²)		27.6±5.7
FEV₁ % predicted		45.4±19.2
MRC (1-5)		3.21±1.35
GOLD (1-4)		2.75±0.90
Median BOD score (Range)		3.00 (0-7)
Median BOD category (Range)		2.00 (1-4)
Median BODAS Score (Range)		6.00 (2-13)
Median BODAS category (Range)		3.00 (1-4)
SGRQ Total%		44.1±19.6

Table 6.4. Baseline characteristics of COPD subjects (Respondents).The BOD and BODAS data are presented as Median (range).

Table 6.5 shows the percentage of responses for those respondents who indicated agreement with the statements of each domain (5 domains; 10 statements in each domain; 50 statements in total) divided into those representing high or low wellness. The results indicate that the majority of COPD subjects show dichotomy in their responses which means they either marked the first two options of the Likert scale (rarely or sometimes) or the last two options (most of the time/always) in response to a written statement, of the questionnaire. For example, all patients responded as either “most of the time” or “Always” against the statement “I experience moodiness/angry outbursts because of my illness”.

Wellness Domains	High Wellness	Low Wellness
PERSONAL / PHYSICAL WELLNESS	I have good appetite & enjoy my food (89%)	I rarely engage in vigorous exercises (71%)
	My liquid intake is adequate (93.3%)	I have negative or critical feelings about myself (52%)
EMOTIONAL WELLNESS	I am flexible and adopt or adjust to change in a positive way. (85%)	I use alcohol as a means of helping me forget my problems (90%)
		I experience moodiness/angry outburst because of my illness (100%)
		I assess my current state of health and stress level on daily basis rarely. (78%)
SELF RESPONSIBILITY- RELATED WELLNESS	I believe my life is in my hands and I control it. (94%)	I am aware that I am responsible for every aspect of my life (58%)
	I believe the way I live is important in improving my health. (93%)	I take a variety of supplements or alternative therapy to help maintain my health rarely (84%)
	I believe I am a major force in determining my rate of recovery from an illness. (94%)	
	I try to perform at least one good deed every day. (74%)	
	I am keen to maintain a healthy lifestyle and healthy diet. (80%)	
MENTAL WELLNESS	I have good sense of wellbeing about my health (70%).	I feel tired or have low energy. (84%)
	I manage my time rather than time managing me. (84%)	I am stressed by my family (90%)
		I am stressed because of my finances. (89%)
		I am stressed because of house work (88%)
		I feel stressed when I go shopping. (95%)
		I feel generally stressed by my bowel habits. (100%)
I am stressed by having to rely on others. (84%)		
SPIRITUALITY	I believe life is a precious gift. (90%)	I rarely go to church or other place of worship. (85%)
	I engage in acts of caring and good will without expecting something in return. (85%)	Practicing my faith rarely occupies an important part in my life. (89%)
		I do not pray for better health. (82%)

Table 6.5.Records of the participants who scored each statement (3-being agreed or 4- strongly agree)

The quantitative analysis of the wellness questionnaire (Table 6.6) with Spearman correlation indicates that a significant correlation was found between Physical/Personal Wellness and other markers of COPD progression such as GOLD (0.006), FEV₁% (0.01), health related quality of life (0.009), multidimensional BOD score and category (0.003 and 0.02) and BODAS score and category (0.02 and 0.002) suggesting the possible role of wellness assessment in these patients and its impact on disease progression. However, other domains of the questionnaire did not show any relationship with any of the relevant and known COPD outcomes measures.

Wellness domains	COPD markers of progression
Personal/ physical wellness	GOLD stage 0.006
	SGRQ score 0.009
	FEV ₁ % 0.01
	BOD score 0.03
	BOD categories 0.02
	BODAS Score 0.02
	BODAS Categories 0.002
Emotional wellness	Not significant
Self-Responsibility related wellness	Not significant
Mental wellness	Not significant
Spiritual wellness	Not significant
Total wellness	Not significant

Table 6.6. Relationship of Wellness domains with COPD markers

6.5. Discussion

Manderscheid defined wellness as mentioned in the introduction of this chapter but wrote about it in terms of its relationship to mental health. Daudey and colleagues (2010) have discussed the SGRQ as an illness measure and have stated that it does not include other aspects related to health status in COPD. The Wellness Questionnaire is an attempt to bridge this gap. Following a literature review and discussion within the research group it was decided to use focus groups to aid in the development of the wellness questionnaire.

Prioritization in health research topics, are mainly driven by professionals. Decision making is influenced by their area of interest, available resources, funding and time. However, patients' involvement in considering and selecting research topics proved to be very useful where patients are considered as expert in that they are experienced in facing, analysing and living

with a disease. Their observations about both apparent and out-of-sight consequences of the disease may be reliable, particularly in chronic illnesses such as COPD.

A focus group is one approach to collecting rich data (McLafferty, 2004) in which the investigator/moderator/researcher/interviewer poses different questions related to the research topic (in the present study questions were about the need for assessing Wellness) to get further understanding of the focus group members' perspective on the topic of discussion (Wong et al., 2008). During the focus group discussions, the interaction of the participants with the moderator as well as with other group members was encouraged.

Initially, the researcher met with the members of Age Concern and this proved valuable in identifying "Spirituality" as an important component of their understanding of a concept of wellness. Subsequently, patients with respiratory problems were the resource relied on and their knowledge, enthusiasm and support for the project was invaluable. The outcome of all the deliberations was the development of the questionnaire.

Unfortunately when the questionnaire was distributed to the members of the cohort only 27 of 134 forms were returned and hence discussion of the results is limited.

Table 6.6 shows that only the physical/personal Wellness domain correlated significantly with the known markers of COPD prognosis. Out of those, BODAS again showed superiority over other indicators. However, other domains of the questionnaire failed to show any significant association. This may be due to the small sample size. The results suggest that more studies will be needed to validate these findings and to draw any firm conclusions.

6.6. Conclusion

This study needs to be considered as a unique addition to research in the field of COPD in that it introduces an assessment of wellness into the management of this illness. However, these results should be regarded as pilot data in that the response rate was very low.

The questionnaire needs to be extensively applied in the clinical environment to further evaluate its relevance and to refine the questions in the various domains.

DISCUSSION

As the findings of each chapter have been discussed at the end of the relevant chapters this final discussion will take an overview of the work presented in the thesis.

7.1 Introduction.

COPD is a complex chronic disease with systemic consequences. These in turn lead to disability often accompanied by comorbidity (Yeo et al., 2006; Lang et al., 2010) and high mortality rates (Gudmundsson et al., 2006). In addition, for spirometric staging of severity discrepancies and controversies exist in relation not only to diagnosis and classification (Harrison 2011), but also to treatment and management (Rabe and Wedzicha 2011). By not having a clear understanding of the stage of the disease, patients' wellbeing could be at risk and healthcare costs could be increased (Bridevaux et al., 2008) with a greater burden put on both hospital and health care workers. However, no clear alternative to impairment of FEV₁ as the marker of severity has yet been defined.

There is therefore a need to adopt a multidimensional approach to the evaluation of COPD patients which also includes an assessment of their inner state of mind including their wellness status. Attitude to the illness appears to play a vital role in the progression of any disease, including COPD and helps to modify patient's attitude, thinking and coping behaviour during their illness.

The use of a combination of all of these assessment tools may lead to an improved outcome in these patients and provide health practitioners with a range of tools for the better management of COPD.

7.2. Cohort Evaluated in this Study.

The present study is unique in several aspects in terms of the cohort used to examine COPD markers. Firstly, the number of female participants in this study (49%) was higher as compared to other relevant studies (Ko et al., 2011; Esteban et al., 2010 and 2011, Li et al., 2010; de Torres et al., 2007). The higher proportion of females in the present study may be due to the increased prevalence of smoking among women in UK. Nonetheless, the higher proportion of females in this study provides the opportunity for health care professionals to consider the findings of this study in relation to both genders.

Another unique feature is the degree of severity as measured by lung function. In the present study the cohort had a mild to moderate degree of lung function decline ($60.9 \pm 20.0\%$) in contrast to other similar studies where the mean FEV₁% predicted were either severe or very severe ranging from 42.5 ± 10.8 to 55.0 ± 13.3 (Celli et al., 2004; Ko et al., 2011; Esteban et al., 2010 and 2011; Puhan et al., 2009; Li et al., 2010; Celli et al., 2004). The lesser degree of severity provided the opportunity to monitor progression from mild to severe disease and their association with other outcomes including mortality and health status.

Patients for this study were recruited from primary care clinics whereas other studies mainly recruit patients from hospital wards or clinics (Ko et al., 2011; Puhan et al., 2009 Celli et al., 2004).

The long term nature of this study also makes it unique. There have been very few studies (Trevor et al., 1979; Leavitt et al., 2006) which examined mortality as an outcome over a 10 year period. Furthermore, the data on historical heights 8-10 year apart were measured and were not based on patient's recall on their highest height. This therefore adds validity to the study findings as regards the use of height as a potential marker.

7.3. Development and Use of Multidimensional Indices

In relation to the assessment of the multidimensional nature of COPD, a major advancement came through a study carried out in 2004 when Celli and colleagues (2004) presented data showing that their multidimensional grading system had a significant advantage over the

Fletcher-Peto model, the classical study used to explain the natural history of COPD. Celli and co-workers (2004) established the BODE index (BODE – BMI, airflow Obstruction, subjective Dyspnoea and Exercise test; a 10 point scale) (Celli, 2004) which proved to be a better predictor of the health outcomes than FEV₁ alone. Later, Puhan and colleagues (2009) developed another multidimensional index (ADO) composed of Age, MRC Dyspnoea index and Airway Obstruction. The index proved as useful as BODE for prognostic assessment in COPD patients. However, by introducing age, the ADO index is compromised because age is the most important determinant of survival, independent of disease status and diagnosis, although its role in any assessment of disease prognosis should not be discarded. Other indices also developed were of limited use. For example Jones and colleagues (2009) developed the DOSE index that contains four COPD related measurements i.e. dyspnoea (D), airway obstruction (O), smoking status (S), and frequency of exacerbation (E). The index proved to be a simple tool to assess disease severity and probability of hospitalisation. There are number of indices developed in the past incorporating various other markers (Van Dijk et al., 2011). Altogether, the indices used 3-8 predictors only one study did not use FEV₁ as a part of the index (Omachi et al., 2008) and only two studies (Omachi et al., 2008; Jones et al., 2009) reported the change over time of the index and the associated outcome.

The present study examines the change over time in the BOD index and other physical markers. Other rarely used markers include blood oxygen (paO₂), knee extensor strength, rate of exacerbations and comorbidities. However, some of the potential (easily measured) markers have not been studied effectively yet; these include smoking status and smoking intensity, lean body mass, hand grip strength and duration of symptoms. This study has investigated some of them and attempted to develop indices that could improve assessment of COPD. To date, only one study (pilot) actually implemented a prognostic COPD index in patient care, without showing significant improvements in health (care) (Gruffydd-Jones et al., 2010). As the practical abilities of COPD indices remain untested, they fail to tackle the current need to improve treatment programs (The Health Foundation, 2007; Schunemann, 2009; Wildman et al., 2007).

The present study has evaluated BOD (BODE without the exercise component) and the results indicate that it is a suitable marker for the measurement of COPD progression and to use in all healthcare settings as well as in the community and/or house bound patients. BOD is a better

marker as many patients particularly with severe COPD are unable to walk. Also, the walk test is not useful in assessing COPD patients with mild disease as they may have normal or above normal exercise capacities (Smith, 2011). It also means that the test cannot be carried out in a primary care setting.

However, there are many other physical measures made on COPD patients and the present study examined a number of other potential clinical, physiological, physical, symptomatic and habitual markers and measurements that could improve the ability of the BOD index to predict COPD outcomes over time. Other potential markers of COPD outcome examined included smoking history, lean body mass, hand grip strength, health status assessment, duration of symptoms, CRP and most importantly the assessment of wellness status which is the new way of evaluating the mental status of these patients.

An initial evaluation of a range of indicators demonstrated that the following were suitable for inclusion in the new index of physical measures developed in this study:

Age

Pack years

Gender

Many studies have examined the role of age in COPD outcomes (Britton et al., 2003; Puhan et al., 2009), but no firm conclusion has been made. However, age adjustment should always be considered in clinical research involving patients with chronic illnesses because of its relationship with mortality (Tran DD et al., 1990) in general and COPD in particular (Britton et al., 2003; Puhan et al., 2009). COPD is more prevalent in people > 45 years and is highest in elderly patients over the age of 65 (Hurd S., 2000, Sullivan et al., 2000). The present study supports previous findings in terms of years of age of COPD sufferers (mean age 69.5 ± 8.7 and 64.5 ± 9.4 in COPD) presented in table 5.2. Our data suggest that patients >73 years of age are highest in the deceased group whereas patients with <57 years are highest in survivors. Further analysis in the present study partially supports the finding of Puhan and co-workers who developed ADO index (Puhan et al, 2009) consisting of Age, MRC Dyspnoea Score and Airway obstruction scores which works better than the validated BODE index in predicting mortality in patients with COPD and underlines the effect of age on 10 year mortality in

patients with COPD. However, age does not alter our principle model of BOD index when age was added as a covariate in the model. However, the current study suggests that consideration should always be given to age when exploring mortality in COPD and other COPD outcomes. The present study successfully proved the value of age which enhances the effectivity of multidimensional assessment when incorporated in BOD.

Tobacco smoke is a well-known risk factor in the development, progression and mortality of COPD and the present research also shows a high prevalence of both current and exsmokers and a high pack-year history in patients with COPD.

The present study supports previous findings (Fletcher et al., 1976; Zaher et al., 2004) that both ex-smoking and current smoking influence disease progression and mortality.

However, avoiding smoking is not sufficient to prevent COPD and the risk factors are not self-same. In eastern countries, the approach to minimize COPD should be different from western countries (Murray et al., 1996). Each individual person has specific risk factors based on economic background, psychosocial status, work related exposure, family and life time medical and drug history.

The findings of the present study thus suggest that the assessment of the smoking status of COPD patients is an essential element and smoking cessation interventions should be promptly discussed with the primary care physician. Therefore, smoking in COPD poses a serious threat to medical world and larger scale researches are needed in order to reduce the impact of this debilitating disorder which influences disease prevalence, prevention, management, treatment, complications, disability and death.

Traditionally, COPD is associated with the male gender; however, over the last decade COPD has become an increasing problem among women (Torres et al., 2010). However, in the present study the numbers of female subjects were higher than males (51% vs 49%) in contrast to other studies such as 14% vs 86% (Ko et al., 2010) and 4% vs 96% (Esteban et al., 2010). Hypothetically, this changing trend of COPD is simply because smoking rates are now becoming higher or at least equal in women compared to men as reflected by the demographical findings of the present study results where the pack-year history is 33.3 ± 25.7 in

men vs 31.1 ± 18.6 in women. Similarly, 52% of females were current smokers in our cohort in contrast to 44% of males. Furthermore, in the analysis of BOD with mortality, the KMSA shows that BOD worked better for females (only over 10 year time-frame) when gender specific analyses were carried out however our findings could not be compared with other similar studies due to the higher number of males in those studies.

Thus it is very difficult to make the judgement that gender itself has a great impact on mortality. However, it is one of the most important factors and should always be considered by exploring the gender based phenotypes of patients with COPD whenever researchers examine COPD outcomes such as mortality, health status and wellness status.

Lean body mass was another potential marker that was evaluated in this study. Unlike previous studies that underlined the role of lean body mass in COPD and other chronic diseases (Schols et al., 2005; Coxon et al., 2004; Engelen MP et al., 1994; Schols et al., 1993). In this regard, however the findings are inconclusive. Reid and colleagues (1992) found a correlation of lean mass with bone mass density (BMD) particularly in postmenopausal females (Reid et al., 1992); however the present study did not consider BMD as an outcome.

Patients with COPD may be quite inactive, not only because of their age but also due to breathing difficulties, a very common subjective complaint in patients with COPD. This problem further leads to impairment in activity which in turn causes muscular atrophy and muscle weakness (Schols et al., 1993, Rantanen et al., 1998). It has been proposed that systemic inflammation has a role in perpetuating damage to muscle (Remels et al. 2007) and exacerbations of COPD are characterised by increased systemic inflammation. (Remels et al., 2007). Also treatment of an exacerbation with oral steroids may contribute to further muscle wasting (Wouters, 2006).

The present study also evaluated handgrip strength as a potential marker of disease progression but it did not appear to be as effective as age and pack years history. Furthermore, this study demonstrated that hand grip strength deteriorates significantly in patients with COPD when measured 12 months apart. The study also found a significant correlation of percent predicted grip strength with some components of Health related quality of life scores measured by SGRQ which is consistent with the findings of previous researches (Ansari et al., 2007). However,

more longitudinal studies are needed in future to evaluate this association, which would really be beneficial with respect to health status, progression and mortality in patients with COPD.

The study suggests that BODAS is the most powerful indicator of mortality as compared to other indices (Figure 5.7 and Table 5.6). The AUC for BODAS was 0.72 ($p < 0.0001$) which is similar to BODE in the Celli study (AUC was 0.74) (Celli et al., 2004). In practice, the utilisation of BODAS has an important advantage over BODE. Due to the nature of the indicators included in the BODAS index which are easily obtainable and measurable in primary care settings and in all patients without any limitations. In contrast, BODE has as one of its component E-Exercise test which requires expertise, resources, patients' motivation and an ability to walk without discomfort. Furthermore, BODAS consists of five different but very basic variables, most of which are modifiable there is therefore more chances of improvement than with BODE.

Thus the addition of age and smoking history to BOD provides an important development and this is clearly demonstrated in the K-M analysis for individual BODAS scores and categories (Figures 5.5 & 5.6). BODAS is therefore a highly appropriate candidate for generalised use when exercise capacity of COPD patients cannot be undertaken. However, the performance of BODAS was not as anticipated in the 2007/8 cohort because of events "death" observed due to a smaller sample size and shorter period of observation (Table 5.7).

Overall, the study suggests that BODAS which consists of five different indicators of COPD progression significantly influences risk of mortality and is also related to HRQL. But it is difficult to inform patients about their chances of survival. However, the scores could possibly be utilized to encourage and also to motivate patients to make efforts to improve their scores by life style changes in order to avoid or to delay any worse possible outcomes and to live healthy life as long as they can.

The present study suggests that age and smoking history could play a vital role in assessing and monitoring progression of COPD particularly when incorporated into the BOD index. On the other hand, the results related to other combinations of markers were not as convincing and therefore further studies may be needed to explore their influence in disease progression and outcomes.

The SGRQ which is the most widely used health status marker in patients with COPD was examined in these patients over time suggesting again that SGRQ is consistently associated with most of the physiological variables and multidimensional assessment indices over time.

Another subjective measurement “Duration of symptoms” was also examined in the present study and demonstrates that this measurement may play an important role in predicting COPD outcomes. However no standard, reproducible and validated instrument is available to accurately record this information that may provide clinically relevant information about the development, progression and outcomes.

The findings of this study suggest a potential phenotype of COPD patients that exhibit no symptoms even in the presence of severe airflow obstruction as measured by spirometry. Similarly, there is another phenotype that has more than 20 years of symptoms. However, no airflow obstruction has been suggested in such a group of patients however no study was found in support of this finding and further research is needed to validate the present study findings.

A biomarker “CRP” that is known to be an important indicator of COPD prognosis was studied in this thesis but the results were not clear and its role in monitoring COPD progression could not be justified. Many studies in the past have suggested the importance of a CRP and its prognostic value in COPD severity and other outcomes (Gan et al., 2004, Dahl et al., 2007). However, the present work did not discover any relationship between CRP levels and other COPD outcomes apart from its elevated level in the COPD groups (on the basis of FEV₁%) with high CRP value (>3mg/dl) in those with FEV₁ > 60% predicted which may indicate CRP’s role in these patients as suggested by a recent study (Stockley, 2009). Although, Stockley’s study (2009) also demonstrated that the increased level of systemic C-reactive protein was related with poorer health status and comorbid conditions (e.g. cardiovascular disease, cancer and skeletal muscle dysfunction).

In order to examine the relationship, various means have been used to investigate the relationship. These included considering CRP as a continuous variable and dividing it into quartiles and cut off values, but in all cases it did not show any significant relationship with any of the COPD outcomes except lung function (when divide CRP values into cut off points of >3 and ≤3) including health status, multidimensional indices BOD and BODE, MRC, history of exacerbation or death.

The study also examined the influence of height variation (loss) on spirometric diagnosis of COPD over time and found that height loss may not only under-diagnose some of the borderline COPD cases particularly in the elderly but also misinterpret the severity of the disease (mild, moderate and severe as per NICE classification of severity) in some cases.

Although many multidimensional indices have been developed and proved useful no consensus has been found as to the use of the most appropriate index to manage patients in primary and secondary care. In other words many indices have been developed for clinical use, as yet, however, these indices lack impact studies to demonstrate effects on patient outcome and health care when implemented in daily patient care. The indices may improve population-based predictions of the natural course of COPD compared to looking at airway obstruction (as measured by FEV₁%) alone, in terms of mortality, hospitalizations and exacerbations. The diversity in populations, (the weighting of) predictors and (the definition of) outcome, strangles any overall recommendations on which index to prefer for predicting prognosis in patients with COPD and how these patients can be motivated to improve their disease.

Clearly, there is a need to explore a patient-centred approach where psychological status comes into play. The present study used this approach and attempted to examine the mental status by means of assessing overall wellbeing including stress factors, their attitude and beliefs and way of thinking when dealing with disease consequences.

7.4. Wellness Status

To date the majority of indices developed for the evaluation of COPD have concentrated on physical, physiological and biochemical measures (van Dijk et al., 2011) however a person's attitude towards their illness can often impact upon the outcome in terms of morbidity and mortality (Sibbald et al., 1988; Kashdan, 2011). In any evaluation of disease progression it may therefore be necessary to include within an assessment index a measure of 'wellness' or their mental attitude towards their illness (Sibbald et al., 1988; Kashdan, 2011; Niemiec et al., 2010).

This study also attempted to explore the deeper picture of the overall health status in these patients with the help of a newly developed "Sunderland Respiratory Wellness Questionnaire"

suggesting the need for its use in patients with COPD to get a deeper picture of the overall health that ultimately has an impact in the form of improved outcomes and better management and prognosis in these patients. In addition, the psychological/wellness status enhances the assessment of overall health status incorporating general, physical and mental health status, which together improves overall health outcomes in these patients.

The key factors that the patients felt impacted upon their wellness was questions related to physical and personal wellness.

Therefore, the management of COPD should be carried out on an individual basis considering personal and social factors that interfere with the progression of this disease. Additionally, how the healthcare workers approach these individuals is also an important factor that needs consideration. For example, generally “stop smoking” is the key target by clinicians to improve COPD related health outcomes. However, attention should also be given on the contributing factors that prevent them from stopping smoking for example health related stress factors, social factors or attitude.

7.5. Combining Qualitative & Quantitative Measures.

Many studies into the development of indices of COPD progression have solely focussed on physical measures (Godtfredsen et al., 2008; Puhan et al., 2009). Few have attempted to assess mental status and its association with COPD progression (Funk et al., 2009; Putman-Casdorph and McCrone., 2009); and health status (Gudmundsson et al., 2006). However to date, no study brings together an assessment of a patients physical symptoms and a measure of their mental attitude (and the factors that impact upon it) in order that both aspects can be managed in terms of the long term management of the illness. The present study explores this phenomenon for the first time.

In all evaluations of disease progression, there is a need to evaluate both physical factors together with “wellness” and attitude. Management of health and the outcome of disease are a mixture of both and a multidisciplinary index should assess both measures. This means a blending of quantitative and qualitative methods. However, in practice, this does not generally occur as studies are either carried out by physicians/clinicians or social scientists.

This study benefited from support from both types of expertise and it has illustrated the need to merge both types of research in terms of the development of future indices for the management of COPD.

7.6. Future Evaluation of COPD.

Following the development and validation of the current indices, the next step for COPD researchers is to perform impact studies (Moons et al., 2009). These studies should establish a firm conclusion in terms of their applicability as well as the impact on health and healthcare and their implementation in primary and secondary care settings. A study is also required that quantifies the effect of using a prognostic index on predefined outcomes including decision making, patient outcome, and cost effectiveness, compared with usual care without implementing the index (Moons et al., 2009).

Another issue is whether or not a prognostic index should integrate predictors, preferably those that can be modified (Schunemann, 2009), and treatments that further improve the index scores, slow the progression and delay worse outcomes such as disability and death (Cote and Celli, 2005; Nasis et al., 2009). Ultimately, indices should be integrated in such a way that self-management strategies can be defined for each individual.

Further work is also needed to explore the variation in BOD scores between 2000-2008 and the ability to predict mortality after 2008. It is a useful idea to identify group of patients who have improved their BOD scores over time and also to explore factors that lead to the improvements in their respective BOD scores/categories that may possibly include dietary modifications, lifestyle changes, regular exercise, attending pulmonary rehabilitation programmes or any other interventions that are beneficial to individuals with improved BOD scores.

Finally, applying a prognostic index in a population other than the one in which it was originally developed may require recalibration or modification. In this regard, Puhan and colleagues (2009) carried out for BODE based on populations. Therefore calibration or stratification of an index allows adjustments that can resolve the dilemma of this strong but

troublesome predictor (Graham et al., 2007). Apart from age, calibration should be carried out for patients with a range of severity and also in patients with frequent exacerbations and patients on oxygen.

The study plays a significant role in the field of COPD management as it provides new multidimensional indices BOD and BODAS for health professionals to assess the clinical impact of COPD in any setting where these patients are being treated. It also helps patients to understand their prognosis and encourage them to modify their lifestyle and improve health status. Furthermore, this study provides a new assessment tool to evaluate the modifiable mental status of these patients that in turn can be used to improve disease outcomes.

However larger cohort studies over a longer time frame will be needed to confirm the findings of the present study. In addition, validation of the newly developed wellness questionnaire and its role in improving outcomes will also be needed in different cohort.

CONCLUSION

The following conclusions can be drawn from the work presented in this thesis:

- The cohort of patients with COPD evaluated in this study was recruited in primary care. They differ from cohort studies reported in the literature which have been mainly identified in secondary care and thus represent a more severely affected group of patients with COPD. The cohort was identified from 1999-2002 and mortality was censored in 2010. The indices developed and evaluated with this cohort were found to be suitable for predicting disease progression and would be suitable for use with patients in the early stages of COPD.
- The index evaluated in this study, BOD, was found to be a suitable predictor of disease progression and outcome. Using KM survival analysis BOD showed better prognostic potential than FEV₁ as recommended in the GOLD/NICE guidance classification of severity, in that there was a higher mortality associated with the highest category calculated using BOD. This superiority was confirmed using ROC analysis. BOD is likely to be a better index for use in a primary care/home setting as it does not include the exercise component found in other indices including BODE, which requires space. The exercise component is also not popular with patients suffering from COPD.
- A number of other physical measures of COPD progression were evaluated and three were chosen for incorporation into the BOD index. Of the three the index incorporating smoking and age, BODAS, had a higher sensitivity on ROC analysis than BOD for predicting ten year mortality.
- Health status as measured using the St Georges Respiratory Questionnaire (SGRQ) correlated with BOD and BODAS but not BODE (all measurements from 2007/2008).

However, SGRQ scores did not show a significant association with three year mortality on KM survival analysis.

- Health status is based on an assessment of symptomatology so the value of examining “Wellness” was explored with a newly designed questionnaire. Focus group research was used to validate and develop the questionnaire to be used with the cohort. A number of areas of importance in terms of the evaluation of ‘wellness’ were identified these included: spirituality and a range of stress factors.
- Although limited results were obtained free comments in the wellness questionnaire identified a range of factors that affect wellness in patients with COPD. These include a range of stress factors which includes environmental stress and the importance of a smoke free atmosphere, the importance of patients being able to manage their illness including the role of nutrition in terms of disease management and the problems of being reliant on other for support.
- COPD is a complex illness with many physical and mental factors affecting the outcome for patients diagnosed with this disease. This study has combined both quantitative and qualitative research in the development of new methods for the evaluation of patients and management of their care. Whilst further research is needed to validate the new index BODAS, together with the newly developed questionnaire for ‘wellness’ the results provide a starting point which will enable health care practitioners to evaluate individual patients and devise care packages that not only manage their physical symptoms but also support their ‘wellness’.

Problems Encountered during the Study

A number of limitations were encountered during the present study. The most important weakness of this study was the high dropout rate (n=179) that eventually reduced the repeat study cohort. However, some of the dropouts were inevitable because of those who unfortunately died. Another reason for drop out was non response either because of an incorrect address on the hospital computers or because they did not wish to participate. (Ethical issues do not allow a researcher to persuade study subjects to participate). Since the data base

was originally established from patients attending COPD and Asthma clinics in primary care and the subjects linked their symptoms with asthma more than COPD it may be possible that some dropped out because patients thought they had asthma and not COPD. .

Another limitation was that the study only examined the ability of the multidimensional index BOD in predicting 10 year mortality in COPD patients and did not examine the recommended index BODE over the full 10 year period. However, the comparison was not possible and/or not applicable to this study because the initial data base was established between 1999-2002 whereas the BODE index was published in 2004. However, the study did perform three years mortality and one year variation between BOD and BODE and their correlation with other COPD outcomes.

Furthermore, the number of respondents for assessing wellness was also very low. The reasons for large number of non-respondents were two fold. Firstly, wrong addresses were used as more than 50 questionnaires were returned back to the researcher. Secondly, there was no verbal contact with the participants prior to sending the wellness questionnaire as this could potentially act as an influencing factor. It was clearly mentioned on the Patient information sheet (PIS) that a home visit can be arranged on the patient's request and contact numbers of all research team members were supplied within the PIS. Nevertheless the response rate was low. Another major contributor was the bureaucratic governance and ethical process recommended by both NHS and the University. It has been stated that UK health research activities are being seriously undermined by an overly complex regulatory and governance environment (The Academy of Medical Science, A new pathway for the regulation and governance of health research January, 2011) This is evidenced by a fall in the UK's global share of patients in clinical trials and other health care researches, and by the increased time and costs of navigating the UK's complex research approval processes.

Recommendations for further work

- ✓ Further valuation of BOD and BODAS as prognostic indicators needs to be carried out in primary care.
 - ✓ Evaluate further the variation in BOD scores and their impact on mortality overtime particularly after 2008 in those with improvement in BOD scores.
 - ✓ Comparison of BOD and BODE in a larger cohort would be useful.
 - ✓ Study BOD in hospital based cohort and relate it to the exacerbations rate and DOSE and ADO index.
 - ✓ Validate the Wellness questionnaire, its reproducibility and its correlation with other tools for assessing health status.
 - ✓ Explore wellness as a concept in other ethnic groups.
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