"DETERMINANTS AND IMPACT OF FATIGUE IN COPD-A ONE YEAR HOSPITAL BASED CROSS SECTIONAL STUDY"

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ACCEPTANCE LETTER

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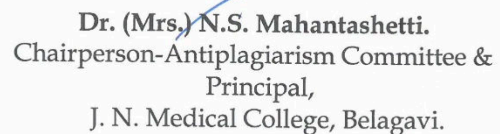

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LIST OF ABBREVIATIONS

COPD - Chronic Obstructive Pulmonary Disease

AECOPD - Acute Exacerbation of Chronic Obstructive Pulmonary Disease

GOLD - Global Initiative of Chronic Obstructive Lung Diseases

FEV1 - Forced Expiratory Volume in 1 second

FVC - Functional Vital Capacity

ERS - European Respiratory Society

ATS - American Thoracic Society

WHO - World Health Organization

HRQOL - Health related quality of life

SGRQ – St.George Respiratory Questionnaire

NHP – Nottingham Health Profile

6MW – 6 Minute Walk Test

6MWD – 6 Minute Walk Distance

GOLD – Global Initiative for Chronic Obstructive Pulmonary Disease

RV – Residual Volume

DLCO – Diffusing Lung Capacity for Carbon monoxide

MMRC – Modified Medical Research Council dypnea grading scale

BODE – BMI, Obstruction of airways, Dyspnea scale, Exercise capacity

CPET – Cardio Pulmonary Exercise Test

PFT – Pulmonary Function Test

CES-D - Centre For Epidemiological Studies Depression Scale

SGRQ - St.George Respiratory Questionnaire

FACIT-F - Functional Assesment of Chronic Ilness Therapy

ABSTRACT

INTRODUCTION: COPD is an important cause that leads to higher mortality in India and

worldwide with airflow limitation, patient with COPD also have systemic manifestation. Dyspnoea and Fatigue are the two most common symptoms experienced by patients with COPD. Association between Fatigue in COPD and health status have been studided in many studies. This study aims at evaluating the determinants and impact of Fatigue in COPD patients.

OBJECTIVE: To evaluating the determinants and impact of Fatigue in COPD patients.

METHODS: This is a hospital based cross sectional study. Stable COPD patients who were diagnosed by spirometry based on GOLD guidelines, after considering inclusion and exclusion criteria were enrolled in the study. Demographic details , MMRC grading , PFT ,6MWD and oral questionnaires i.e FACIT –F , CES-D, SGRQ were conducted on the same day.

RESULTS : 100 stable COPD patients who visited Respiratory OPD in KLEs Dr.Prabhakar Kore Hospital & MRC were evaluated. A vast majority of study population was Men (81%) , most of them were smokers with mean age being 61.73± 9.72. Fatigue severity was significantly associated with smoking (p <0.0001), COPD duration (r=-0.8334, p <0.0001) , BMI (P =0.0038) , previous hospitalization (P <0.001) and GOLD staging (p<0.0001), FEV1 (<0.0001).

CONCLUSION : Severe fatigue was found to impact on patients , dyspnoea level (MMRC) (P<0.0001) , Excercise capacity (6MWD) (r=0.6562 , p<0.0001) , QOL (SGRQ) (P<0.0001) and it also leads to depression (p<0.0001).

KEY WORDS : COPD , FACIT-F , CES-D ,SGRQ

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INTRODUCTION:

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and alveolar abnormalities usually caused by significant exposure to noxious particles or gases.[1]

COPD is the third leading cause of death worldwide, causing 3.23 million deaths in 2019 , Over 80% of these deaths occurred in low- and middle-income countries (LMIC). Environmental exposure to tobacco smoke, indoor air pollution, and occupational dusts, fumes, and chemicals are important risk factors for COPD[2].

The prevalence of COPD is more in countries where smoking is highly prevalent and vice-versa. Sadly, smoking is turning out to be on the rise in India.It has been estimated that 2500 Indians die everyday from smoking related causes-one every 40 seconds[3,4]. In India it has been estimated that 65% of all men use some form of tobacco(about 35% smoke, 22% use smokeless tobacco and 8% use both). With the fact that smoking is on the rise , it is safe to assume that the incidence of COPD is going to increase in the years to come.

Dyspnea and fatigue are the two most common symptoms experienced by patients with COPD . The most important complaint of patients with COPD is dyspnea. Another accompanying important symptom of dyspnea is fatigue in COPD.

Fatigue is commonly defined as a subjective, un-pleasant symptom which incorporates total body feelings ranging from tiredness to exhaustion creating an unrelenting overall condition which interferes with individuals’ ability to function to their normal capacity[5].

Fatigue ranks second to dyspnoea as a symptom contributor to decreased quality of life in COPD patients[6]. Dyspnoea and fatigue are a subjective experiences that can only be measured from the patient's perceptions, because every person have different thresholds for noticing, reporting, and rating the severity of these symptoms[7].

Moderate to strong positive relationships have been reported between fatigue and mood states such as anxiety, irritability and depression, and sleep quality[8] .

In primary care populations, patients with fatigue receive a lifetime diagnosis of depression or anxiety more frequently than those without fatigue and there appears to be a longitudinal relationship between the severity of fatigue and impaired functioning and psychologic symptoms[9].

Association between fatigue and health status, depression have been reported in many studies. However there is no study mentioning as to what are the factors that determine the level of fatigue in COPD patients and its impact of the daily life of COPD patients.There is no Indian study done so far evaluating the determinants and impact of the sutdy. the This study aims at finding the determinants and aims of the fatigue .

OBJECTIVE OF THE STUDY

- To evaluate the determinants and impacts of fatigue in stable COPD patients .

REVIEW OF LITERATURE:

DEFINITION OF COPD :

Global initiative for chronic obstructive pulmonary disease (GOLD) defines Chronic obstructive pulmonary disease (COPD) as a common , preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and alveolar abnormalities usually caused by significant exposure to noxious particles or gases.

The ATS and ERS[10] define COPD as a preventable and treatable disease state characterized by airflow limitation that is not fully reversible. The limitation of airflow is progressive and is associated with abnormal inflammatory response of lungs to the noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects lungs, it also produces significant systemic complications.

COPD BURDEN :

Globally 65 million moderate to severe COPD cases are present according to the estimate of World Health Organisation[11].

In People above 30 years the incidence is 11.4% globally. It is higher among Men 14.3% and 7.6% in women. Regionally ,according to WHO it is Higher in America with 14.1% and least in the SouthEast Asian region with the prevalence of 7.8%[12].

Previously prevalence was more common in men, but lately due to urbanization and more exposure to air pollution, the prevalence is equal almost in both women and men across the globe[13].

The valuation of the exact prevalence of COPD is challenging owing to the various methods used in studies such as use of self-report questionnaire, spirometry , GOLD, ATS/ERS criteria and age group analyzed.

The prevalence of COPD as estimated by National health and Nutrition Examination Survey in US population aged 6-79 Years by Pre and Post bronchodilator Pulmonary Function Test is 10.2 to 20.9% . The prevalence was also found to be less after using the post bronchodilator criteria(33%) [14]

In Latin American cities the prevalence was found to be 7.8% to 19.7% using spirometry as described in the PLATINO – a project done in the obstructive lung disease investigation[15].

In India ,the COPD prevalence has increased from 3.3% to 4.2% according to the estimate in 2016[16].

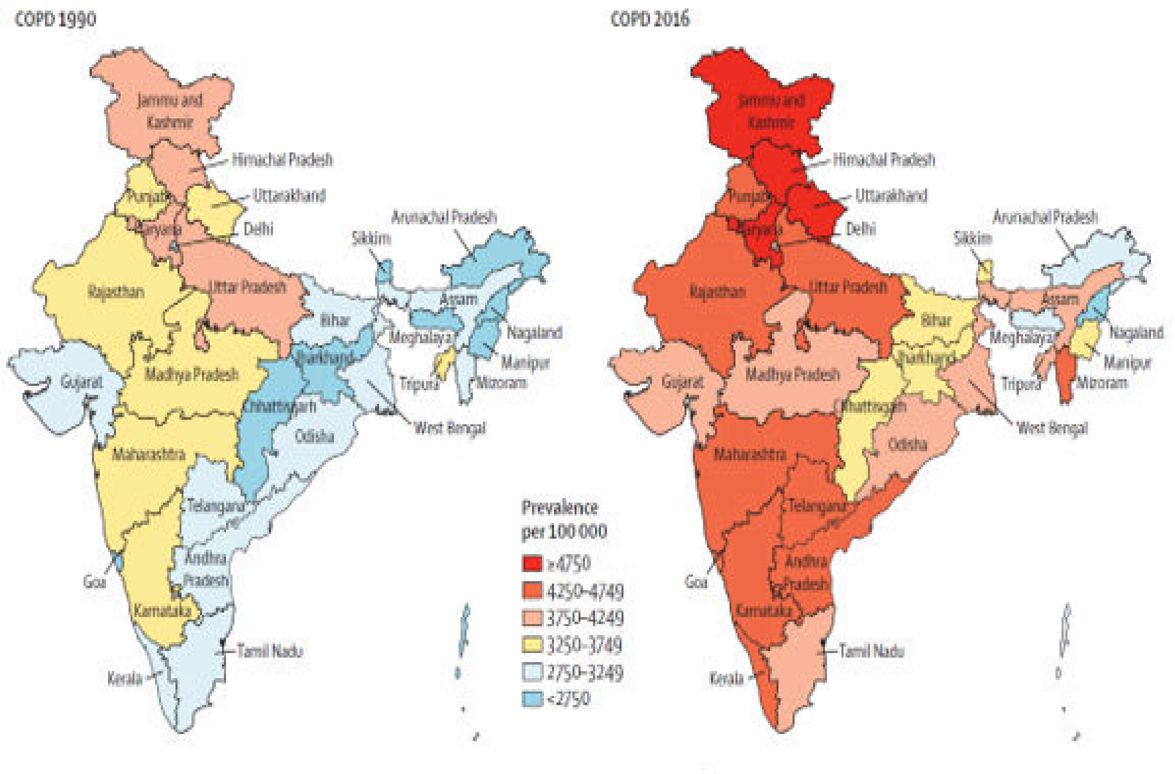


FIGURE 1: PREVALENCE OF COPD IN INDIA

The burden of obstructive lung Diseases(BOLD) is an on-going study to assess the prevalence of COPD. So far the trial has been completed in 29 countries which showed a prevalence of COPD grade 2 or higher of 10.1% (SE 4.8) overall,11.8%(SE-7.9); for men, and 8.5%(SE-5.8) for women[1]

THE COST BURDEN OF COPD :

Apart from the health impact of the disease, the economic burden is always high with loss of billions every year. In India, The estimated economic loss due to COPD is about Rs.35,000 crores for the year 2011 and around Rs.48,000 crores for the year 2016.[17]

A Canadian report that registered 790 COPD patients with an exacerbation. Out of which 151 required hospitalization, they projected an average charge of US$ - 9,557.[17]

Similarly, a Swedish study[18] estimated the the cost of COPD exacerbations to be SEK 2,111 and SEK 21,852 respectively. Another study with cohort of 2,414 COPD patients, found that the average cost of an Acute Exacerbation of COPD was US$159.[19]

Lakium et al[18] estimated the cost burden of COPD in southern INDIA. The total direct cost of medicines in a COPD patient accounted to be Rs.29,885 ± 11,995.33 and the total mean indirect medical cost was Rs.7,441.25 ± 2,228.90.[18]

Another study which was conducted in North India has found the cost of Burden due to COPD treatment to be Rs.33,354 to Rs.63,642. The hospital cost (71%) accounted for the maximum and the least percentage is associated with the transport (2%).[20]

RISK FACTORS :

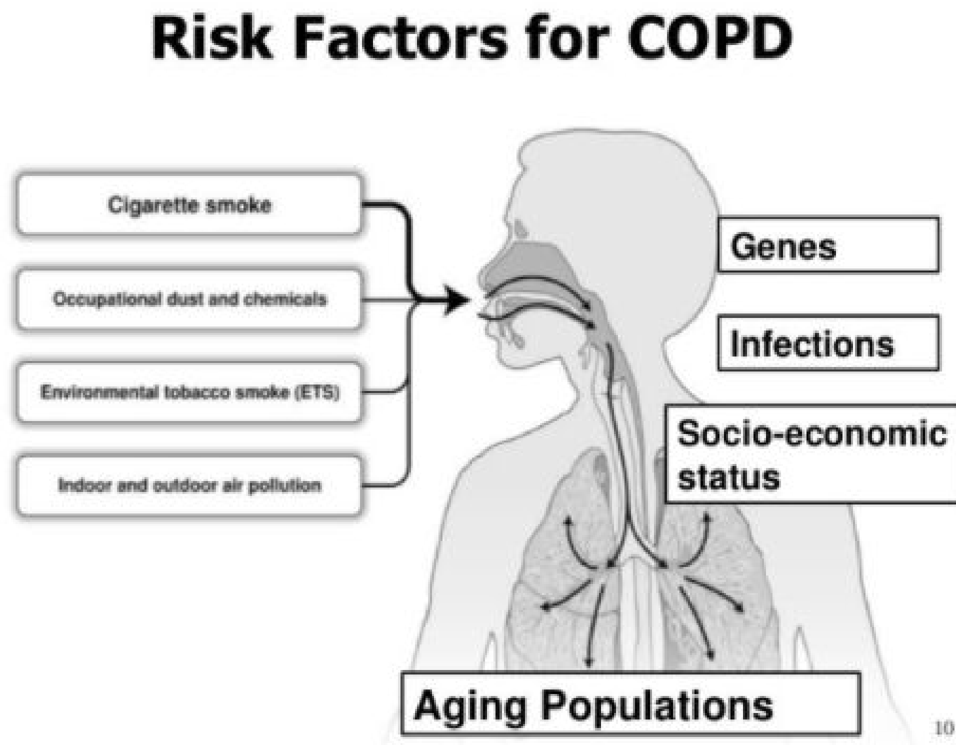
Knowledge regarding risk factors help in preventing the disease initiation and progression.

Risk factors are broadly classified into host factors and environmental factors.

TABLE 1. Risk factors of COPD

HOST FACTORS	ENVIRONMENTAL FACTORS
Genes	Smoking
Asthma/Airway hyper reponsiveness	Air Pollution
Age	Occupational exposure
Gender	Childhood respiratory infections
	Low Socio Economic Factors

FIGURE 2: RISK FACTORS FOR COPD



1. **<u>Genetic susceptibility</u>** :

COPD develops as a result of complicated gene-environment interaction. Hereditary deficiency of gene, alpha 1 antitrypsin, an inhibitor of serpin peptidase, clade A, member 1 (SERPINA1) the best documented genetic factor of COPD. Few other genes responsible for COPD includes Glutathione S Transferase[21] , Tensin 1 (TNS1) , C terminal domain (GSTCD) , hydroxytryptomine (serotonin) receptor 4 (htr4) , advanced glycoslylation end product-specfic receptor (AGER) , thrombospodin type 1 domain containing 4 (THSD4)[22], metalloproteinase 1 and metalloproteinase 2.

2.Asthma / Airway hyperresponsiveness :

Chronic asthma may be a risk factor to cause COPD . As studied by Vonk et al[23] 16% - 20% asthma patients were found to have airflow limitation which was irreversible.

3. Age and Gender :

As per a study done in USA COPD prevalence among the age group <44 years and those of >66 years increased from 3.2% to 11.6%.

So according to this study among the various factors responsible for COPD, age is one of them[25]. With the changing lifestyle like smoking and chewing of tobacco, COPD prevalence is equally seen in both genders nowadays unlike what used to be the prevalence 10 years ago[24].

4. Smoking :

Around the globe , cigarette smoking is the common reason for COPD. They have symptoms like breathlessness, cough , wheezing , greater reduction in FEV1 and other abnormalities in lung function than that of the non smokers[25]. Various reasons for COPD in non smokers could be atmospheric irritants , chemicals , gases , organic and inorganic particles. Smoke and bio mass fuel circulating in a kitchen with poor ventilation can also be a factor for COPD etiology[26,27]. E-cigarettes which are used as a de addictions to cigarettes also can cause COPD, albeit the incidence is less compared to cigarettes. The prevalence of COPD in E-Cigarette users is 4.45% as per a recent study[28].

5. Air Pollution :

There are primary and secondary pollutants of air in the atmosphere which includes smoke from vehicle, industries , wastes burning and other sources. These pollutants cause COPD by bronchial hyperactivity and oxidative stress[29]. Second hand

smoke or environmental smoke is another risk for COPD. It causes lung injury by degrading body elastin[30]. Few studies state that these pollutants may have an impact in childhood lung development and increase exacerbation rate, but sont have a significant effect on COPD pathophysiology[31].

6. <u>Childhood respiratory infections</u> :

Reapeated infections during childhood can cause reduction in lung function and increased symptoms later during adulthood[24]. But the infection role in COPD is still not very clear. Tuberculosis is another risk factor for COPD.[31]

7. <u>Low socioeconomic status</u> :

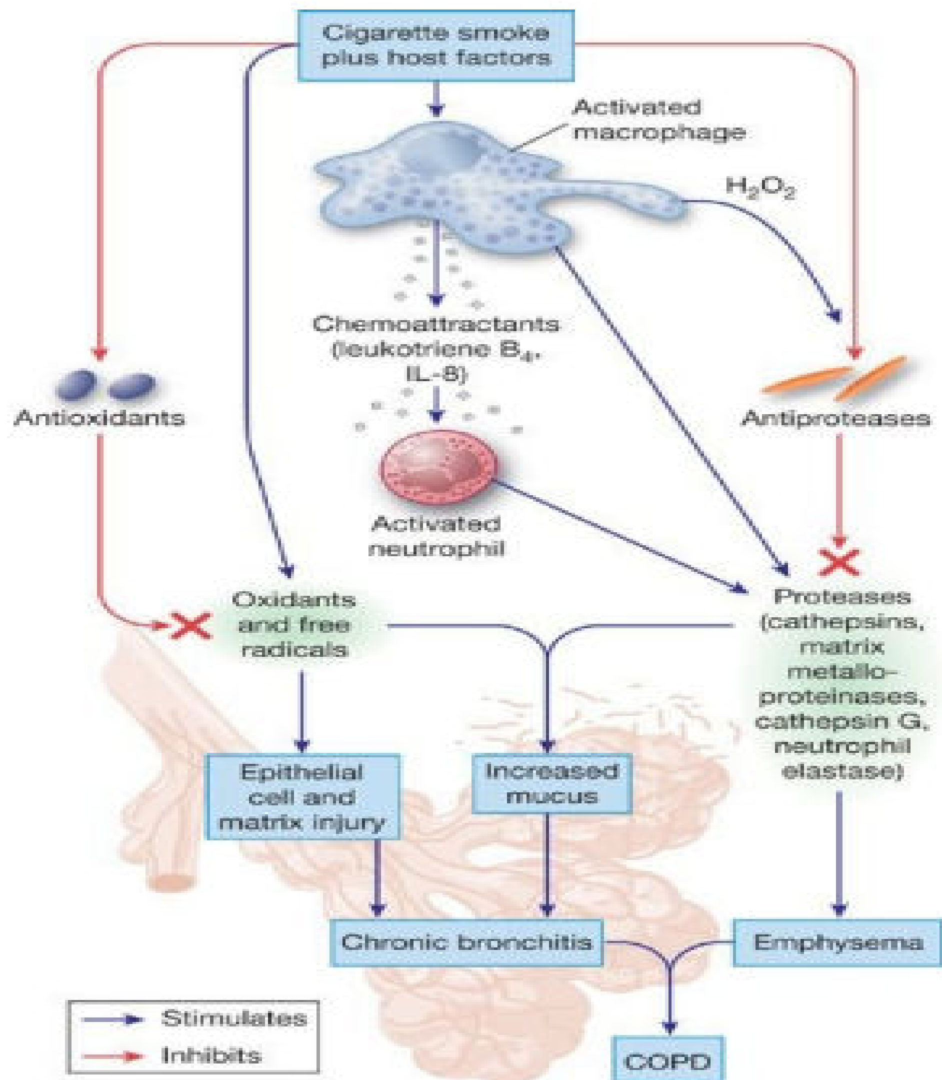
Simultaneous outdoor and indoor pollutions , overcrowding, poor nutrition , infections can lead to COPD. There are no strong evidence indicating the increased prevalence of COPD in the lower socioeconomic group[32].

PATHOGENESIS :

COPD is a condition with complex change in the structure and function of alveolar tissue along with small airway. Narrowing and damage to lung parenchyma and alveolar attachments of airways and smaller airway remodeling are two major causes for COPD. Few major pathogenetic process which leads to this pathway are

1. Inflammation
2. Protease antiprotease imbalance.
3. Oxidative stress.

FIGURE 3: PATHOGENESIS OF COPD



1. **<u>Inflammation :</u>**

Irritants and inhaled substances like air pollutants or gases or cigarette smoke activate surface macrophages and airway epithelial cells to release multiple chemotactic agents like chemokines which in turn attracts circulating neutrophils, monocytes and lymphocytes in the lung. This inflammatory process is thus a self perpetuating mechanism for COPD[33].

Tumour necrosis factor alpha (TNF alpha), Interleukin 1 (IL-1),IL-6,IL-8 and Transforming Growth factor Beta (TGF beta) along with chemokines like CXCL 10 and CXCL 11 which cause small airway fibrosis are the inflammatory mediators released by activates epithelial cells of the airway . They recruit T cells leading to further activation of macrophage and metalloproteinases release causing further inflammation. Goblet cells produce mucous and anti oxidants , antiproteases along with defensins which are the defense mechanism of the airway epithelial cells. They are impaired with further inflammation[33].

Cigarette smoke or any other noxious particle activate Macrophage which in turn release inflammatory mediators like TNF alpha , CXCL 1 , CXCL 8 , reactive oxygen species (ROS), and secrete enzymes like MMP 2 , MMP 9 , MMP 12 causing pathological destruction.

Activate macrophage also release chemotactic factors which have a direct stimulatory effect on granulocyte production and neurophil recruitment in the airways. These neutrophils secrete serine proteases including neutrophil elastase, cathepsin G , MMP 8 , MMP 9 with alveolar destruction.

2. **Protease Antiprotease imbalance :**

Stimuli like cigarette smoke, noxious particles produce oxidative stress and release inflammatory mediators which cause inflammation. It also inactivates several antiproteases like SLP, alpha 1 antitrypsin by oxidation which causes protease anti protease imbalance and leads to further progression of inflammation[34].

3. Oxidative stress:

When excess of ROS is produced in view of anti oxidant defense, it results in harmful effects like damage to proteins , lipids and DNA[1]. Also , this oxidative stress reduces the antioxidant level due to downregulation of Nuclear erythroid factor (NRF2) which helps in increasing the production of antioxidants,further reducing anti oxidants.

PATHOPHYSIOLOGY:

Inflammatory injury to lung parenchyma, airways and pulmonary vasculature in different combinations leads to exaggerated work of breathing, airflow obstruction and gaseous exchange abnormalities which are characteristic features of COPD. Advanced COPD leads to Pulmonary arterial hypertension, Cor-pulmonale or Right heart failure. Airflow limitation is usually seen in the expiratory phase which is characteristic of COPD patients and represents the final expression of various derangements of respiratory mechanics.

1. Airflow limitation and air trapping :

The expiratory phase airflow limitation is the principal physiological defect in COPD.

Intrinsic airway factors relate to bronchial wall remodeling/ fibrosis and increased mucosal secretions. Extrinsic factors cause loss of elastic tissue support for small airways and therby leading to dynamic compression during the expiratory phase[1].

Hyperinflation in COPD leads to increased Functional residual capacity (FRC) which relates to the amount of air which remains in the lung at the

end of tidal exhalation. This is turn leads to gas trapping and increase in Residual volume (RV). As a result there is an increase of the work of breathing which serves as an important factor for dyspnea. As expiratory time is important for lung emptying , factors like increasing respiratory rate during exercise results in increase in FRC or delayed emptying[34].

2. **Ventilation perfusion abnormalities** :

Abnormalities in gas exchange results in hypoxemia and hypercapnia . Reduced ventilator drive leads to reduced ventilation which in turn causes co2 retention and it Is further exaggerated by increased work of breathing causing severe airflow obstruction and hyperinflation along with severe ventilator muscle impairment[1].

3. **Mucous hypersecretion** :

Chronic airflow irritation in chronic bronchitis causes goblet cell hyperplasia and enlarged submucosal gland leading to chronic productive cough. Most of the inflammatory mediators and proteases trigger mucous hypersecretion.

4. **Ventilatory muscle dysfunction** :

Many factors contribute for ventilator dysfunction in COPD. As a result of hyperinflation muscle strength and endurance of inspiratory muscles have a mechanical disadvantage. Few other factors which lead to added limitation of exercise capacity are nutrition depletion, tissue hypoxia, and loss of muscle mass[35,36].

COPD AS A SYSTEMIC DISEASE :

COPD is a condition with permanent and progressive airflow obstruction with extra pulmonary manifestation[37]. Many epidemiological studies and clinical trials have helped in understanding the importance of comorbidities[38].

Another study by Antonelli-Incalzi [39] et al showed that the impact and prognostic role of comorbidities in COPD. From their data analysis from 270 patients discharged after a COPD exacerbation, they found common comorbidities associated with this disease. They are Hypertension which had an incidence of 28% , diabetes had 14% and ischaemic heard disease which is 10%. The median survival was 3.1 years and 228 patients out of 270 died during a 5 years follow up period. So it is essential to manage extrapulmonary abnormalities with airflow limitation caused by the disease.

DIAGNOSIS :

1. **Medical history:**

   A detailed history evaluating the risk factors, allergic history, asthma , sinusitis, any family history of allergic disorders, repeated childhood infections, symptom pattern, effect of disease on lifestyle, no. of hospitalization, other disease, effect of disease on lifestyle, social and family support and drug history also to be taken.

2. **Physical examination :**

   Physical examination gives a detailed idea about hyperinflation, disease severity,presence of respiratory failure and cor pulmonale or congestive cardiac failure.

3. Spirometry :

Spirometry is essential to diagnose COPD. As per GOLD criteria a post bronchodilator value of ≤ 0.7 and it is an objective measure of airflow limitation.

4. Imaging :

a) chest radiograph :

chest radiograph is done routinely to rule out diagnosis other than COPD. Changes of COPD in CXR include flattened diaphragm, hyperinflation,tubular heart,increased retro sternal space,hypelucency of lung fields and pruning of pulmonary vasculature.

b) CT scan of Thorax :

CT scan of the thorax might help when the patient is being planned for surgeries like lung volume reduction surgery and it is also useful in the differential diagnosis [34,40].

5. Static lung volumes and DLCO :

Body plethysmography is useful in identifying air trapping and static hyperinflation which helps to know the disease severity. Calculating the diffuse lung capacity gives information about the functional impact of emphysema in COPD[41].

6. **Oximetry and Arterial blood gas analysis :**

Pulse eximetry helps in knowing the patients oxygen saturation and the requirement of oxygen supplement. An spo2 of <92%should be investigated with Arterial blood gas[42]. ABG gives information about identification of respiratory failure and further management.

7. **Alpha 1 antitrypsin screening :**

Alpha 1 antitrypsin deficiency is genetic disorder. Screening for its deficiency is advocated in countries with high prevalence of COPD[43]. These patients usually have involvement of lower lobe predominantly and their age is usually >45 years. When the serum concentration is less than 15-20% of normal it is highly suggestive of homozygous alpha 1 antitrypsin variants[1].

8. **Disease severity assessment** :

Disease severity assessment is done to determine

1) Amount of airflow obstruction.
2) Impact of the airflow obstruction on the overall health condition of the patient.
3) To identify the future risk of conditions like exacerbations,oxygen requirement, hospital admission and death.

Determination of these factors helps in the planning of treatment.

Lung function test abnormality and disease severity:

According to GOLD 2021[1], severity of disease is classified according to PFT and it is :

TABLE 2 : Classification of disease severity according to PFT:

GOLD Staging	Grading	FEV1 % predicted
1	Mild	≥80%
2	Moderate	50-80%
3	Severe	30-49%
4	Very severe	<30%

Numerous studies have seen a weak relation between FEV1% and symptoms with impairment of life [44,45].

Nature and intensity of patient's current symptoms:

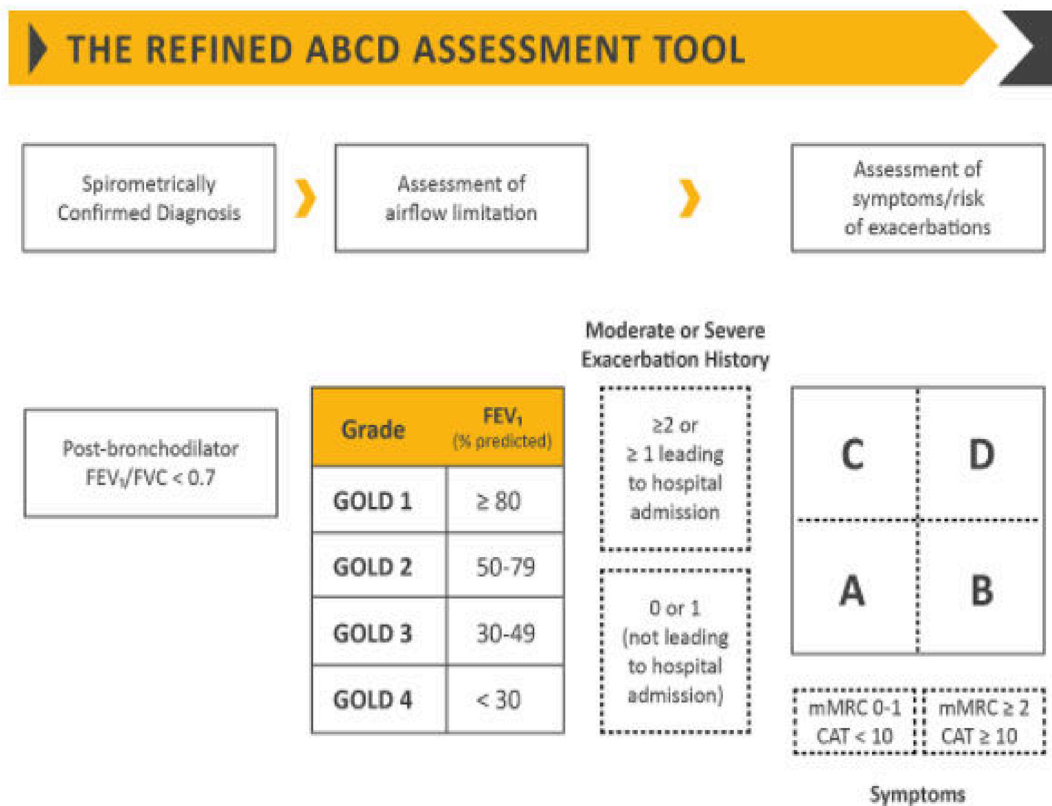
Since it was thought that breathlessness was the chief complaint of COPD , MMRC scale was used to know the severity of the disease. However COPD is known to have several other symptoms apart from breathlessness[46]. So detailed assessment of symptoms is done by scales like Chronic Respiratory Quesrionnaire, St.George respiratory Questionnaire (SGRQ)[47]. These scales are sensitive than other questionnaire like Clinical assessment Test (CAT) and COPD clinical Questionnaire (CCQ).

Presence of any Comorbidities :

COPD is a condition predominantly involving the elderly with multiple Comorbid conditions. Other comorbidities seen with COPD includes cardio vascular diseases,skeletal muscle dysfunction, anxiety,depression, metabolic syndrome, osteoporosis and lung carcinoma[48]. COPD by itself might increase the risk for other diseases like lung carcinoma[49,50]. This again might be due to other common risk factors (eg.smoking) , genetic susceptibility or impaired clearance of carcinogens.

Co morbid condtions are seen with patients with any amount of airflow obstruction[24]. This again can influence the mortality and hospitalization independently[51], which requires specific treatment along with COPD treatment.

FIGURE 4 : COPD ASSESMENT AS PER GOLD 2021



Moderate or severe exacerbation history:

- ≥2 or ≥1 causing hospital admissions
- 0 or 1 (not causing hospital admission)

Symptoms (more in A and B)

- mMRC 0 – 1 , CAT < 10 (A and C)
- mMRC ≥ 2, CAT ≥ 10 (B and D)

1. BODY MASS INDEX :

COPD patients are often observed to have nutritional deficiency. Loss of weight in COPD patients who visits OPD ranges from 20% and it is about 35% in hospitalized patients[52].

It was also observes that low BMI could be a risk factor for mortality in COPD patients[53].

2. Obstruction of airways :

It is an objective test done by spirometry. FEV1/FVC ratio of <0.7 indicates that there is obstruction. According to the FEV1 values grading of severity was done.

As per GOLD 2021 guidelines, it is classified as :

TABLE 3 : FEV1 and severity of obstruction :

Predicted FEV1	Severity of obstruction
>80%	Mild
50- 79%	Moderate
30-40%	Severe
<30%	Very severe

3. **Modified MRC dyspnea scale**[54] :

The most common symptom seen with COPD patient is breathlessness. This is the common reason for patients to seek medical attention[55]. MMRC scale is a simple scale to measure the level of breathlessness and disability while doing an activity. Albeit being a good scale it is nowadays considered as a primitive method of assessing symptoms since breathlessness is not the only symptom of COPD.

TABLE 4 MMRC DYSPNOEA SCALE :

MMRC0	I only get breathless with strenuous activity
MMRC1	I get short of breath while hurrying on the level or walking up a slight hill
MMRC2	I walk slower than people of the same age on the level because of my breathlessness or I have to stop for breath when walking on my own pace on the level
MMRC2	I stop for breath after walking about 100 metres or after a few minutes on the level
MMRC3	I stop for breath after walking about 100 metres or after a few minutes on the level
MMRC4	I am too breathless to leave the house or I am breathless when dressing or undressing

4. **SIX MINUTE Walk Distance (6MWD) :**

Six Minute Walk test (6MWT) is an accurate and simple test for assessing the severity of the disease and exercise tolerance in a COPD patient. It has gained popularity due to its simplicity ,reliability, and standardization[56]. Different factors reduce 6MWD like shorter height, female sex ,lack of motivation,impaired cognition, cardio pulmonary or musculo skeletal diseases. Thus it helps in predicting survival and ranking the disease severity[57].

The main advantage of this test is the measurement of functioning of muscles along with measuring the fatigue in individual group of muscles or specific muscles. Milder disease patients may not show reduced exercise capacity.

FATIGUE IN COPD:

Fatigue is the perception of physical or mental weakness due to exertion which can be a common symptom in COPD[58,59], and it is also associated with low health status, dyspnea[60,61] and depression.

There are various studies evaluating the perception of fatigue in COPD[60,61]. Inspite of these, there are differences in the interpretation and evaluation of fatigue, leading to confusion and difficulty in comparison between various studies . The perception of fatigue can be defined in various ways as tiredness[62], shortness of energy[63], exhaustion or weakness[64].

Various Studies describe fatigue in different of ways: it may be one of the symptoms of the disease [66,67], as patient complaint[65], is subjective multicomponent experience[61,68], as component of General Health measure [69,70], or as an isolated variable affecting many areas of patient health and functioning[62,71]. Fatigue can be considered as an independent phenomena with variable manifestation like physical or mental tiredness, loss of concentration, attention or motivation[74].

The prevalence of fatigue in in COPD :

There are only few studies regarding the prevalence of fatigue in COPD ; however differences in the methodology between studies resulted in two different results. The important factors include disease severity and stability , time from last exacerbation, comorbidities and differences in evaluation of fatigue itself.

One study [66] reported high fatigue prevalence of 91% patients where they complained of experiencing fatigue for minimum sometimes and 43% " almost always" and "always". Although patients in this study were reporting fatigue as a feature of an exacerbation restricting the generalization to a stable population; in addition there was poor characterization of the patient. With the same tool Graydon et al[73] evaluated 71 severe COPD patients at a 6 monthly interval for a period of 2.5 years. The prevalence of Fatigue in the set of patients was initially 59% and 62 % during final assessment and it did not increase significantly over time. This idea supports the presence of lower (yet clinically relevant) levels of fatigue during a period of relative stability.

Walke and co-workers[74] evaluated the fatigue symptom using the m0dified Edmonton Sympt0ms Assessment Scale (ESAS) in 74 C0PD patients, and followed these patients after a period of 24 months. Fatigue, along with dyspnoea and physical discomfort, were the most common symptoms. The fatigue prevalence was 69% (moderate to severe (50%)) at the end of the study.

A Study done by peters et al [75] Included 168 moderate to severe COPD patients haing a mean age of 64.5. checklist individual strength (CIS) was used as a subscale for measuring fatigue. Abnormal fatigue score (>26) was seen in 47% of the patients which included 24.4% severely fatigued patients. Furthermore, most of the patients (n=77)were followed up after 4 years. In this sub cohort the percentage of abnormal fatigue increased from 45.5% to 63.7% during the follow up. Fatigue level was found to be increased in 30% of patients and severe fatigue was seen in 41.6%. This study gave the longest fatigue follow up period data, illustrating an increase in fatigue over time. These changes in prevalence can be attributed by the difference in co morbidities and also severity of the disease between studies or during the follow up period.

Another study explored the symptom burden and Quality Of Life (QOL) in advanced COPD[76]. This study investigated 100 COPD patients with profound airway limitation using the Memorial Symptom Assessment Scale (MSAS). The device assessed severity ,frequency, prevalence, severity and extent of symptoms and included lack of energy subscale. The most prominent symptom was lack of energy followed by shortness of breath and it was reported in 71% of the patients.

The prevalence of fatigue ranged from 35% in newly diagnosed patients, 48% in mild COPD, 58%-69% in previously diagnosed patients, 71% in in patients having advanced disease, 92% during disease exacerbation and 96% in in palliative care patients. The fatigue Prevalence in COPD increases with time along with the disease advancement. Preference and perception of fatigue in COPD is clearly dependent upon authors definition, assessment method and or or disease severity . However the importance of assessing fatigue clinically may be undermined presently[77].

SUBJECTIVE FATIGUE COMPARISON BETWEEN PATIENT WITH COPD AND HEALTHY OLDER ADULTS :

A basic question related to fatigue in COPD pertains to age adjusted norms i.e whether or not fatigue is a feature of the disease or is it merely a orbiter dictum of aging process. This doubt had been sought to be cleared in two independent studies which proclaims fatigue to be an independent feature of COPD.

Baghai-Ravary and colleagues[71] studied 107 patients with moderate COPD along with 30 healthy control subjects. These 2 groups have been adequately matched according to age and other factors. Patients with significant history of other diseases are excluded from the study.

Fatigue was assessed from the Functional Assessment of Chronic Ilness Therapy (FACIT-F) scale. In this study population COPD patients had markedly low scores when compared to healthy subjects suggesting that higher levels of fatigue are not related to age. However this unidimensional tool provides only general results about fatigue and gives scarce information about particular aspects like mental and physical components.

Leweko et al[78] did a multidimensional study in 74 mild-to-severe patients and 35 healthy age matched subjects. In this study Multidimensional Fatigue Inventory (MFI-20) was used to measure 5 different components of fatigue like physical, mental, general, reduced activity and motivation. Their study implied that all the dimensions of fatigue are profoundly impaired when compared to the healthy age matched normal subjects.

GENDER DIFFERENCES IN FATIGUE IN COPD:

Theander and Unosson[79] did a study which investigated fatigue with respect to gender in COPD patients and healthy subjects. 345 COPD patients (150 male) were advised to complete the Fatigue Impact scale which denoted fatigue in terms of frequency, duration and severity. No significant difference was found between the two gender of COPD subjects when compared to the findings of normal healthy subjects.

FREQUENCY AND PATTERN OF FATIGUE IN COPD:

The question as to how often does fatigue occur and whether there is any diurnal variation warranted a research study.

A study done by Shephard et al on 104 COPD subjects showed , fatigue was identified as “lack of energy”. There were on an average 2.7 reports per week of fatigue[67].

In another study done by Lamb et al[63], fatigue was reported to occur everyday, intermittently throughout the day. In advanced disease, frequency of ‘lack of energy’ is similar to that of breathlessness; 67% of patients decribed it as ‘frequently’ or ‘almost constant’[76].The daily pattern of fatigue is difficult to find out. However a study done by McCarley et al demonstrated the temporal variations of symptoms in COPD[80]. It studied the pattern of fatigue over 8days. Using a Visual Analog Scale patients were asked to rate their Fatigue at 5 points a day.

A circadian rhythm pattern was identified. Peak fatigue was found in patients at 16.16hr, with a 95% confidence interval ranging from 14.36 to 17.40 hours.

DETERMINANTS OF FATIGUE IN COPD :

Many studies focused on identifying the causes of fatigue in COPD using standardized questionnaires[61-62,65,68,71,81-82]. The use of Uni and multidimensional measures has influenced presented results. Few other studies have identified Association between fatigue and other variables on the basis of simple Coefficient correlation which cannot be as robust as a multivariate analysis.

Generally these studies reported an association between fatigue and breathlessness[61,65,68,81-82]. Marked correlations were identified between unidimensional measures of fatigue and breathlessness irrespective of the severity of disease[62,65,81]. They also significant mild-to-moderate correlation between all dimensions of Multidimensional Fatigue Inventory (MFI-20) and baseline dyspnea index, wherein lower scores denotes higher dyspnoea (r= -0.27 for mental fatigue tp-0.53 for physical fatigue)[68]. Studies have a limitation with the lack of multiple regression analysis and confounder adjustment. So these results are indicators of direction rather than being a predictors of fatigue.

Kinsman and colleagues[66] used dyspnea severity classification similar to MMRC scale possible relation between fatigue and dyspnea severity. Significant differences were found in the frequency of fatigue between the groups. The findings of this study is similar to another study[70] where fatigue was assessed

using the FACIT-F questionnaire and significant differences in fatigue according to MMRC scale was found. In another study using MFI-20[78], differences according to MMRC dyspnea grades were found only for selected dimension and were not present for mental fatigue and reduced motivation.

Recently association between fatigue (Manchester COPD-Fatigue scale) and a range of inflammatory markers (IL-6,CRP,TNFα ,TNF α-R1 and TNF α-R2) in 120 moderate COPD patients were studied[82]. No significant correlation was found between fatigue and any of the markers. However, Borg exertion score after a walk test correlated weakly with TNFα and CRP (r=0.24, p=0.19,p=0.05, respectively).These findings may suggest that even though chronic fatigue is not directly related with systemic inflammation on COPD, there is ceratin degree of association between this inflammation and acute sensation of tiredness at rest/exercise.

The combination of several psychological and physiological factors maybe because of fatigue, which reflects the multidimensional nature of fatigue.
Only few studies assessed the predictors of fatigue using multivariate analysis. Thus a combination of depression exercise capacity, muscle strength , airway limitation, blood oxygenation, BMI, dyspnoea and sleep quality predict different dimensions fatigue related to COPD.

IMPACT OF FATIGUE ON COPD PATIENTS HEALTH :

Fatigue was identified as an important and common symptom of COPD patients, which might have a negative impact on their functional and health status.
In patients with mild to moderate COPD increase fatigue is associated with higher sick leave from work and higher frequency of future exacerbations[62,71]. Recent study showed that higher VAS fatigue was associated with higher disability level in in COPD patients[83]. Fatigue showed negative Association with the functional performance[62,84]. However it is not certain that in what way fatigue contribute to impairment in patients functional performance.

A Study done by Kapella et al[62] show that fatigue, airflow limitation, anxiety ,mood directly affected patients functional performance.

Further research shows that patients with COPD show the combination of breathlessness and fatigue, which leads to a gradual decline in their activities of daily living (ADLs)[63]. Though fatigue directly did not interfere with family law any other relationship it limited social roles.
However ,in a recent study it was found that abnormal fatigue levels affect functional impairment, QOL, and relationships in COPD patients[75]. Thus it impacts patients outside home activities. In one study fatigue was the only predictor of reduced time spent outdoor[71].

Moerover patients who reported significant fatigue limitations in cognitive, physical and psychosocial functioning and had worse health-related QOL compared to those without fatigue. The impact of fatigue QOL in COPD has been repeatedly

evaluated by authors showing significant relationship between was fatigue and reduced QOL[61,71].

DEPRESSION IN COPD:

Significant number of COPD patients have depression. Both COPD and depression are frequently associated with poor physical activity, withdrawal, anhedonia, fatigue, poor appetite, sleep disturbances and difficulty regarding concentration which has a greater impact on the outcome of COPD[85].

A cross sectional study done by Van Ede et al showed that point prevalence of Depression in COPD ranged from 7% to 42%[86]. The prevalence of depression in India varies from 21% to 83% and one study from south India found that prevalence of depression is 25.7% in population more than 60 years[87].

Another study done by Jamal et al[88] observed that patient with COPD have a heavy burden of respiratory distress, physical disability in daily activities and poor quality of life.

An Indian study which studied prevalence and the risk factors in 126 stable COPD patients found that educational status, BMI, FEV 1, respiratory symptoms, physical impairment and dyspnea were the potential predicators of depression in COPD patients[89].

METHODOLOGY :

MATERIALS AND METHODS

- **Source of data:**
- In Department of Respiratory Medicine at KLE'S Dr.Prabhakarkore Hospital and Medical Research centre, Nehrunagar, Belagavi, Karnataka between January 2020 - December 2020.

Method of collection of data:

- **Study design**: Cross sectional study.
- **Study period**: Jan2020 - Dec2020
- **Sampling method:** consecutive sampling- Every subject meeting the inclusion criteria until the sample size is met.

Sample size formula:

- **Sample size**: $N= z^2pq/d^2$
- N: Sample size
- **Z:1.96 rounded off to 2**
- **p**: The prevalence of the condition
- **q :**(100-p)
- **d** : The precision of the estimate 10% of p
- p: 8% in BELAGAVI
- q: 100-p=92
- d: 1.2
- N=100

INCLUSION CRITERIA:

- **Stable COPD** patients(without acute exacerbations for atleast 8weeks prior to study) whose age **>40 years** with FEVI/FVC <70% (post bronchodilator).

EXCLUSION CRITERIA:

1) Bronchial asthma.

2)Cardiac patients suffering from congestive cardiac failure or unstable angina or recent MI.

3)Any major life threatening illness

4)Patients who are unable to perform spirometry or 6 minute exercise test.

5)Bronchogenic carcinoma

6)Neurological disorders.

METHODOLOGY :

- The subjects were enrolled in study after they give informed written consent. A detailed history was taken regarding patient age, sex, past medical surgical history. After considering inclusion and exclusion criteria patient will be taken up for study.

- Patients included in study was assessed based on variables like Body mass index which is measured by knowing height and weight. Airflow obstruction will be measured using spirometry which is being performed 15minutes after the inhalation of 400mcg salbutamol according to ATS guidelines.

- The **FACIT-Fatigue**[90] is a simple 13 point questionnaire which provides a validated measure of the level of fatigue in COPD patients. The response to each question was measured on a scale of 0-4, and scored such that the minimum overall score of 0 reflects the highest level of fatigue measurable and the maximal score of 52 reflects the lowest possible level of fatigue. A higher FACIT-Fatigue score indicates less fatigue.

- The **CES-D**[91] is a 20 point questionnaire which assesses the prevalence of depression and magnitude of change and associated symptoms in COPD patients. The CES-D is a 20-item scale commonly used to evaluate current depressive symptom severity, with a score range of 0–60 (higher scores reflect increased symptom severity). Item responses range from 0 to 3, where 0 = rarely or none of the time (less than 1 day in the past week), 1 = some or a little of the time (1–2 days), 2 = occasionally or a moderate amount of the time (3–4 days), and 3 = most or all of the time (5–7 days).

- Exercise capacity was assessed with six minute walking test**(6MWD)**[56,57]. Experience of dyspnoea will be measured by modified Medical Reseach Council **(mMRC).**

- Health status of the patient will be measured using **St.George Respiratory questionnaire (SGRQ)**[92] . It measures health status (quality of life) in patients with diseases of airways obstruction. Scores are calculated for three domains, Symptoms (Part 1), Activity and Impacts (Psycho-social)(Part 2) as well as a total score. Scores range from 0 to 100, with higher scores indicating more

limitations. Generally COPD patients have SGRQ scores ≥25 and scores <25 are usually found in healthy people[93].

The impact of fatigue in COPD patients was measured through CES-D which measures the prevalence of depression in COPD patients, SGRQ which measures the health status, mMRC which measures level of dyspnoea and 6MWD which measures the exercise capacity.

Statistical Analysis

Statistical analysis will be performed with SPSS version 19 software package. The results of the study will be analysed and presented as numbers, percentage or mean ± standard deviation (SD). Student t test, analysis of variance (ANOVA) and Chi-square will be used for comparison between groups. The correlations will be analysed by Pearson correlation coefficients. A p value less than 0.05 will be considered significant for statistical hypothesis testing.

RESULTS :

TABLE 5 : BASELINE CHARACTERISTICS OF THE PATIENTS

VARIABLE	MEAN	SD
AGE (YEARS)	**61.73**	**9.72**
COPD DURATION	**11.63**	**3.87**
FEV1	**0.57**	**0.13**
FVC	**53.83**	**24.24**
FVC %	**61.64**	**15.78**
FEV1/FVC	**0.57**	**0.13**
6MWD	**312.84**	**80.13**
MMRC	**1.97**	**1.36**
BMI	**21.6**	**3.68**
SGRQ (PERCENTILE)		
Symptom score	**35.05**	**12.77**
Activity score	**36.04**	**16.24**
Impact score	**13.15**	**3.64**
Total score	**28.08**	**9.45**
DEPRESSION		
MILD	**17.88**	**0.93**
MODERATE	**23.29**	**0.11**
SEVERE	**46.18**	**8.44**
FATIGUE		
MILD	**48.02**	**1.35**
MODERATE	**38.97**	**4.06**
SEVERE	**20.75**	**4.45**

Above table shows complete demographic details of the study population. Mean age was 61.73 ± 9.72 . **Duration of the disease in the study group was around 11.63** ± 3.87 years.

Mean FEV1 was 0.57 ± 0.13. FEV1/FVC ratio was around 0.57± 0.13 with most of the study population in moderate and severe groups according to GOLD 2021 guidelines . Mean six minute walk distance was 312.84 ± 74.76 meters. Mean MMRC was 1.97 ± 1.36 . On an average BMI of the study population was normal i.e 21.6 ± 3.68. The SQRQ score was 28.08 ± 9.45

AGE WISE DISTRIBUTION OF PATIENTS:

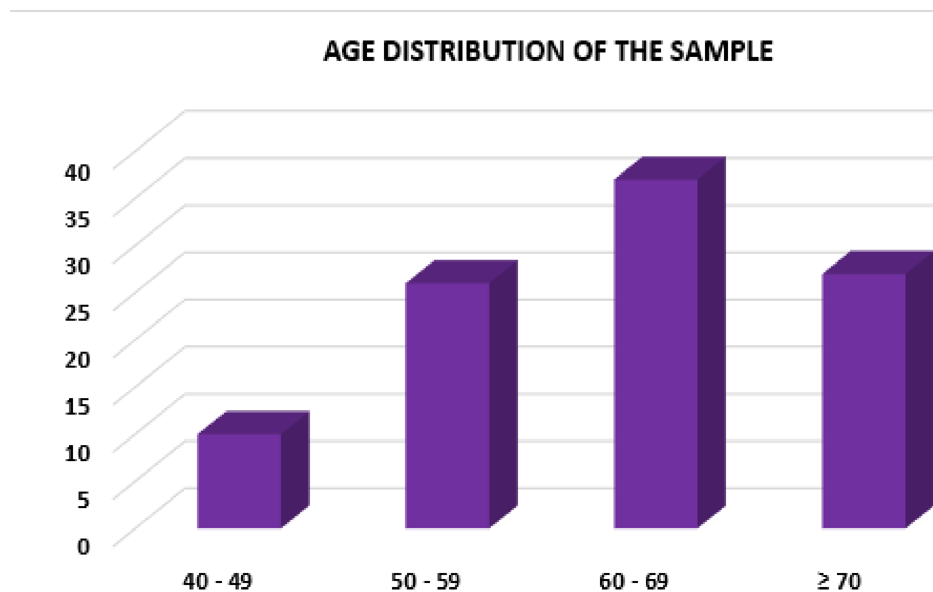
TABLE 6:

AGE	NUMBER(%)
40 - 49	10
50 - 59	26
60 - 69	37
≥ 70	27
TOTAL	100

TABLE 7:

AGE			
MEAN	S.D.	MINIMUM	MAXIMUM
61.73	9.62	42	85

FIGURE 5:



The mean age of the study population was 61.37 ± 9.62 years. The minimum age being 42 years and the maximum being 85years. Most of the patients in this study were 60-70 years of age that is 37%.

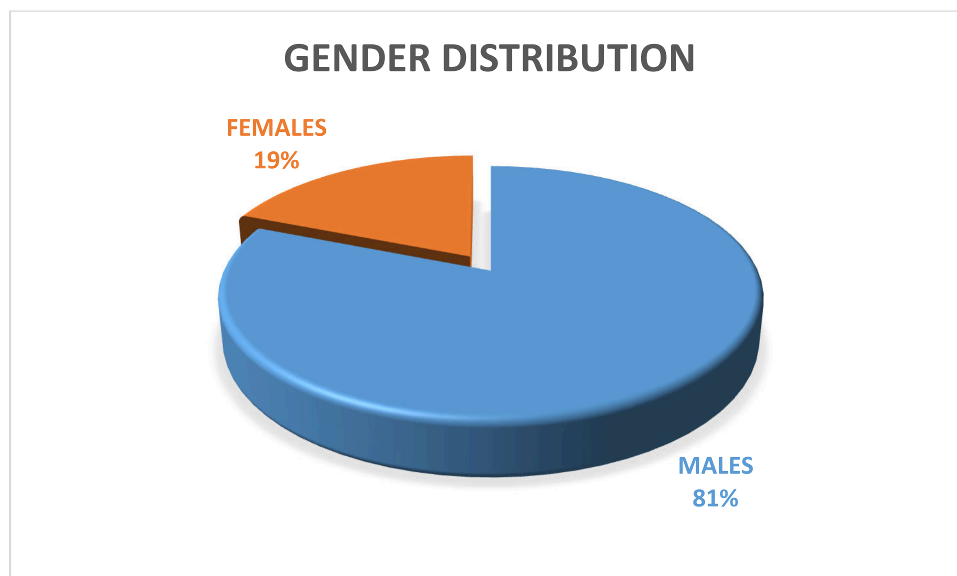
GENDER WISE DISTRIBUTION OF THE PATIENTS :

TOTAL NO. OF SUBJECTS- 100

TABLE 8:

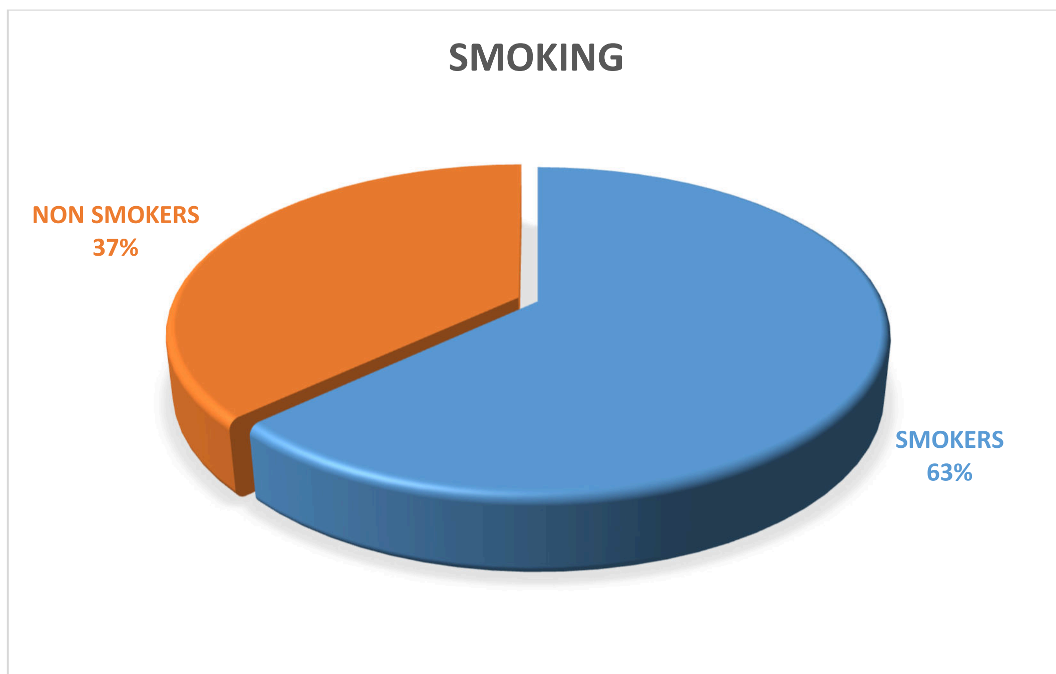
GENDER	NUMBER (%)
FEMALES	19
MALES	81
TOTAL	100

FIGURE 6:



81% of the patients were male and 19% of them were females. There was a predominance of male gender in this study.

FIGURE 7: DISTRIBUTION OF PATIENTS ACCORDING TO SMOKING HABIT



63% of patients were smokers. So many patients included in the study were smokers.

FIGURE 8 : DISTRIBUTION OF PATIENTS ACCORDING TO ALCOHOL HISTORY

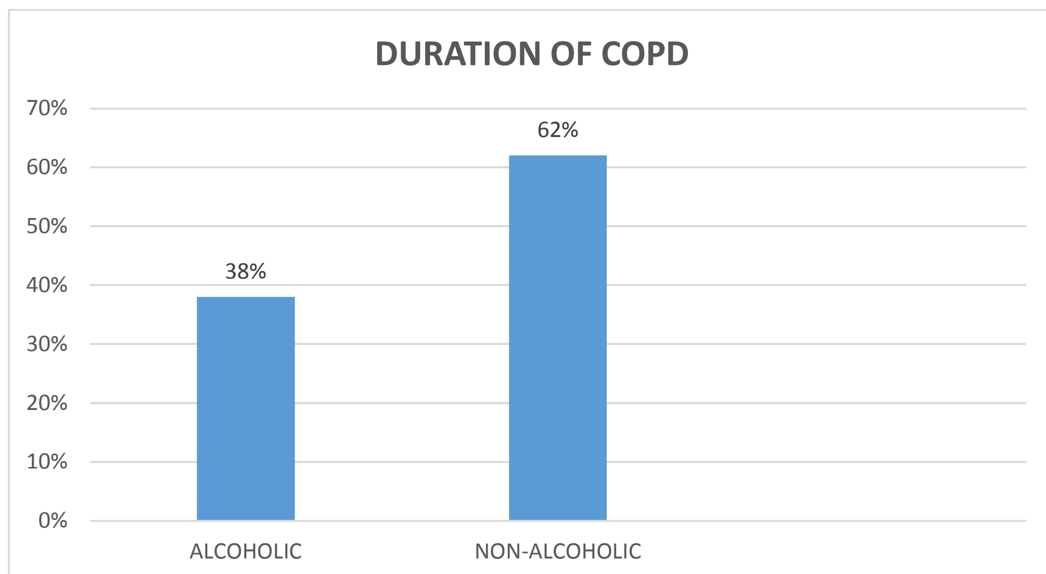
61% of the study population gave history of alcohol intake. Majority of the study population has a history of alcohol intake.

DISTRIBUTION ACCODING TO DURATION OF COPD

TABLE 9:

DURATION OF COPD	NO. OF PATIENTS (%)
< 10 YEARS	53
10 – 20 YEARS	37
>20 YEARS	10

FIGURE 9: DISTRIBUTION ACCORDING TO COPD DURATION



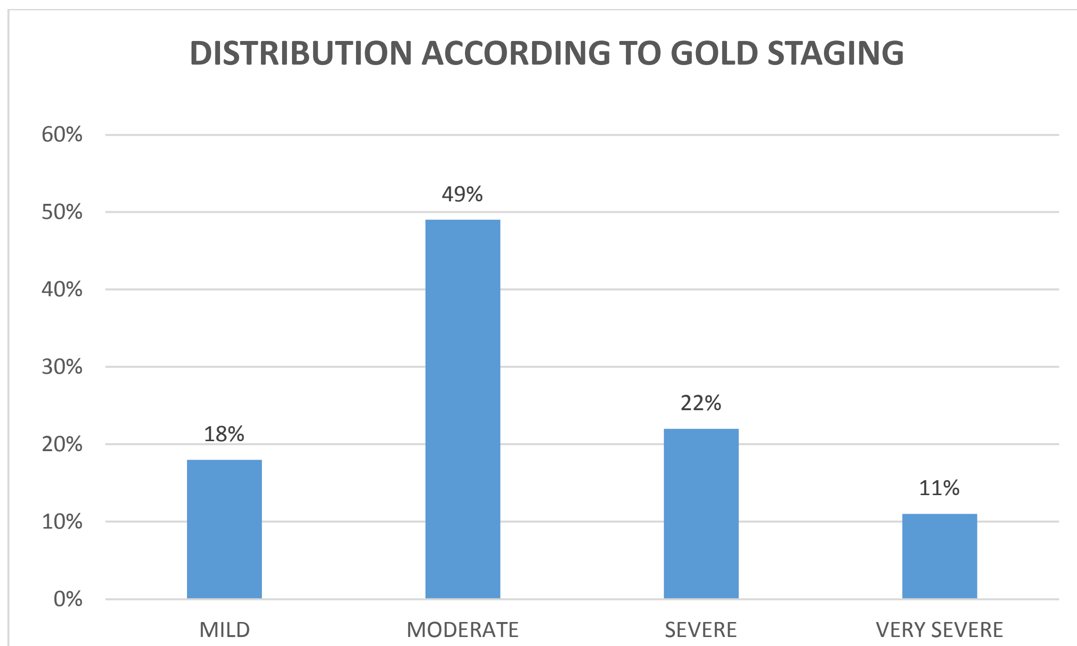
In this study group 53% of patients had COPD for a period of <10 years, 37% had COPD for a period between 10-20 years and 10% of them had COPD for more than 20 years.

DISTRIBUTION OF PATIENTS ACCORDING TO GOLD STAGING :

TABLE 10:

		AGE	
GOLD STAGE	NO. (%)	MEAN	S.D.
MILD	18	50.06	5.70
MODERATE	49	59.90	6.27
SEVERE	22	69.36	7.05
VERY SEVERE	11	73.73	4.47
TOTAL	100	---	---

FIGURE 10: DISTRIBUTION ACCORDNIG TO GOLD STAGING



18% of the patients were in the COPD mild category , 49% were in the moderate , 22% of them in severe and 11% were in the very severe category of GOLD staging.

TABLE 11 : DISTRIBUTION ACCORDING TO CO-MORBIDITIES

CO MORBIDITIES	NO. OF PATIENTS (%)
DIABETES	58
HTN	51
IHD	21

58% of the patient had diabetes, 51% patients had HTN and 21 patients had IHD. Hypertension was the most common prevalent comorbidity in this study followed by diabetes.

FIGURE 11 : DISTRIBUTION BY COMORBIDITIES

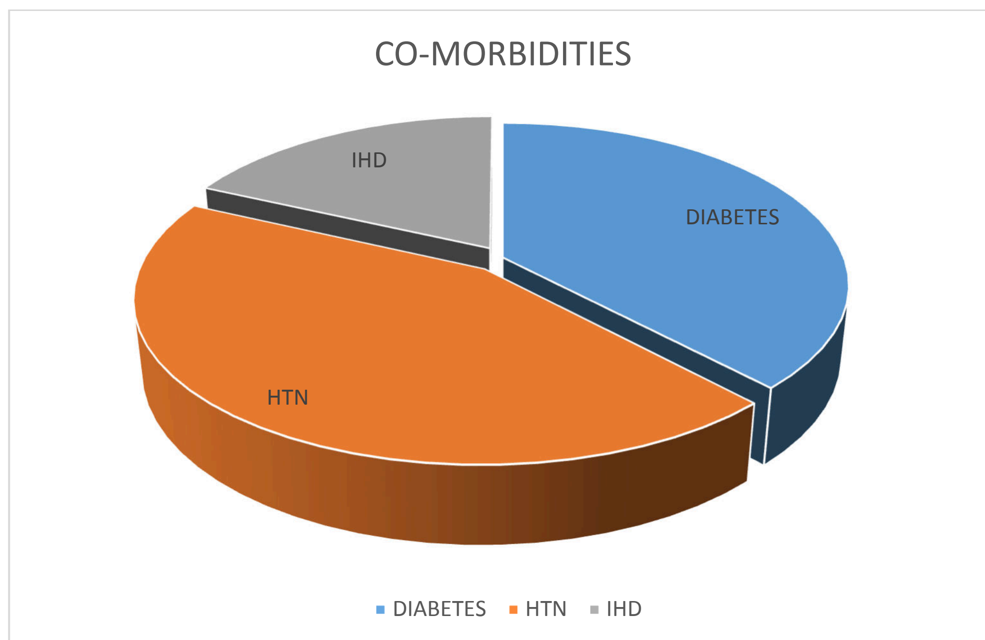


TABLE 12 :

DISTRIBUTION OF PATIENTS ACCORDING TO BMI :

BMI	NO. OF PATIENTS (%)
UNDER WEIGHT	21
NORMAL	63
OVER WEIGHT	14
OBESE	2
TOTAL	100

Most of the study population (63% patients) were in the normal BMI group . 21% patients were in the underweight group , 14% in the overweight group and 2% of them in the obese group.

Mean BMI of the study population was 21.63 ±3.68.The maximum BMI was 31.2 and the minimum being 16.1

FIGURE 12 : DISTRIBUTION OF POPULATION WITH RESPECT TO BMI

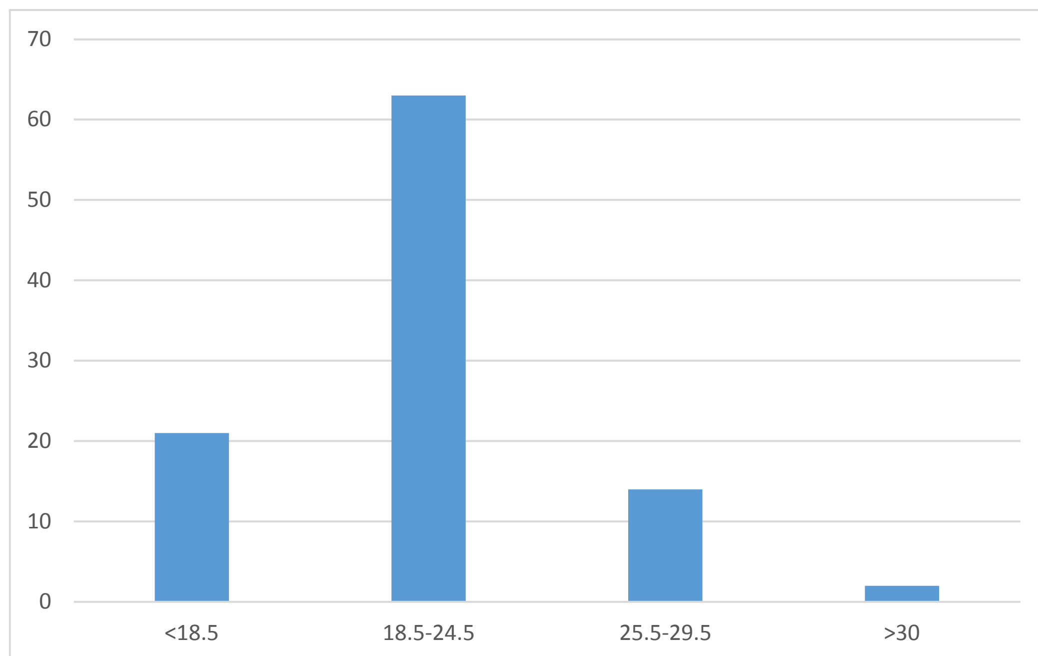


TABLE 13 : CLASSIFICATION AS PER MMRC :

MMRC GRADING	NO. OF PATIENTS (%)
0,1	54
2	31
3	14
4	1

MMRC classification of the study population showed that 54 % of the patient were grade 0,1. 31% of the patients had grade 2, 14% of the patients had grade 3 breathlesness and only 1 patient had grade 4 MMRC.

Most of the study population had grade 1 or 2 MMRC breathlessness.

TABLE 14 : HOSPITALISATION IN THE PAST YEAR :

NO. OF ADMISSIONS	NO. OF PATIENTS (%)
0	43
1	36
2	19
3	2

57% patients gave hospitalization history in the past year. 36% had only one admission. 19% had 2 admissions. 2% of the patients had 3 admission in the past year.

FIGURE 13 : DISTRIBUTION ACCORDING TO NO. OF ADMISSION

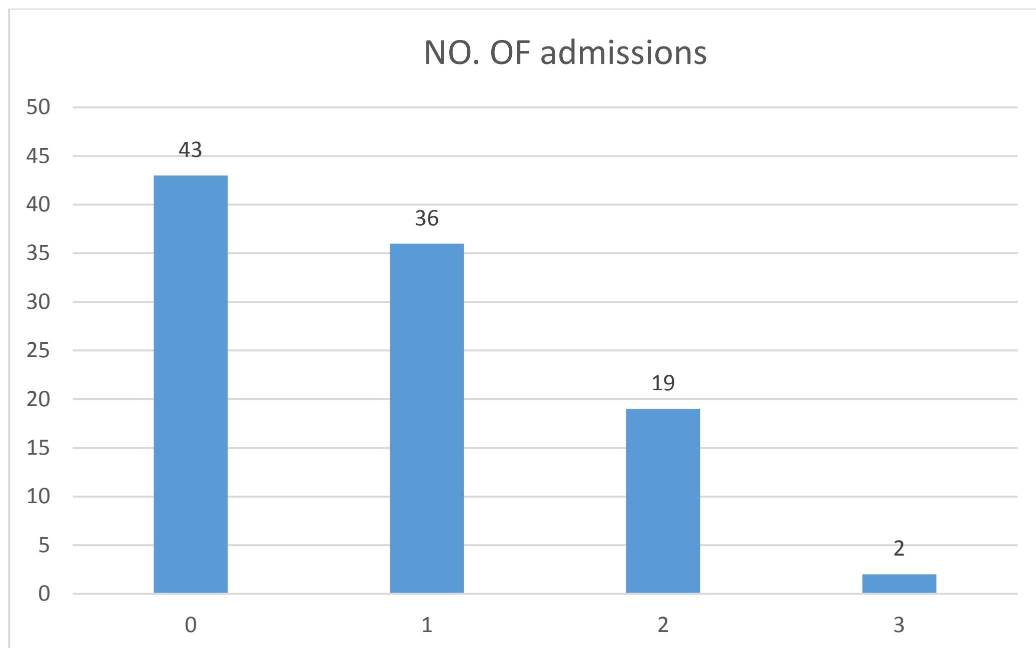


TABLE 15 : DEPRESSION PREVALENCE AND DISTRIBUTION :

STATE OF DEPRESSION	NUMBER(%)
WITHOUT DEPRESSION	48
WITH DEPRESSION	52
TOTAL	100

Among the study population , 52 % of the patients were found to have and 48% of patients did not have depression.

FIGURE 14 : PREVALENCE OF DEPRESSION

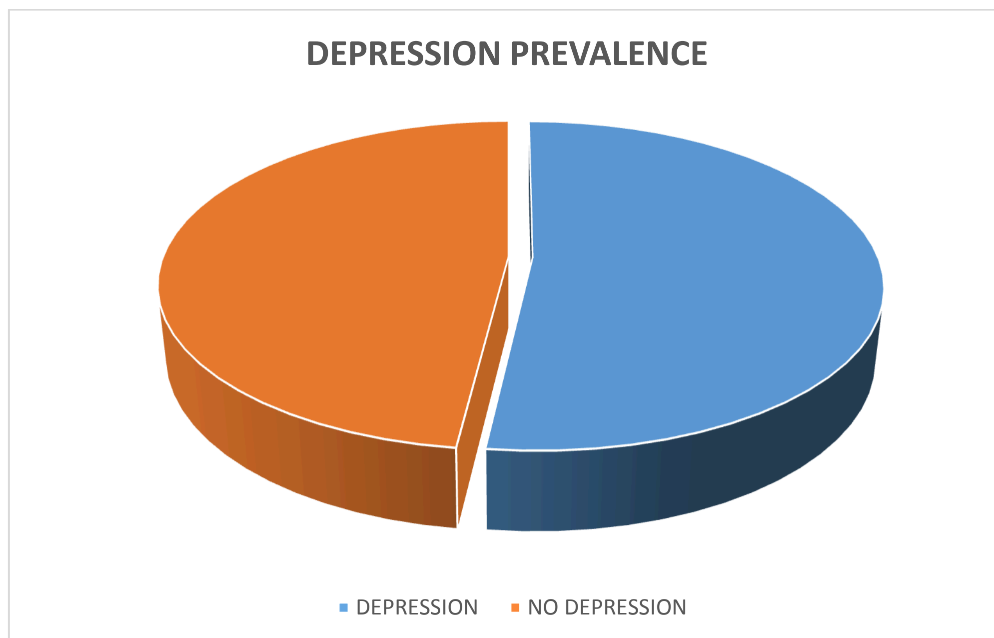


TABLE 16 : STAGEWISE DISTRIBUTION OF DEPRESSION ACCORDING TO CES-D SCALE

		FATIGUE	
STAGE OF DEPRESSION	NO.(%)	MEAN	S.D.
NORMAL	48	45.71	5.66
MILD DEPRESSION	17	39.00	5.36
MODERATE DEPRESSION	7	39.29	5.50
SEVERE DEPRESSION	28	25.29	10.39

17 % patients had mild depression with the depression score of 17.88 ± 0.93 ; 7 % patients had moderate depression with depression score of 23.29 ± 0.11 and 28% patients had moderate depression with a score of 46 ± 8.44 according to the CES-D scale

FIGURE 15 : STAGEWISE DISTRIBUTION OF DEPRESSION ACCORDING TO CES-D SCALE

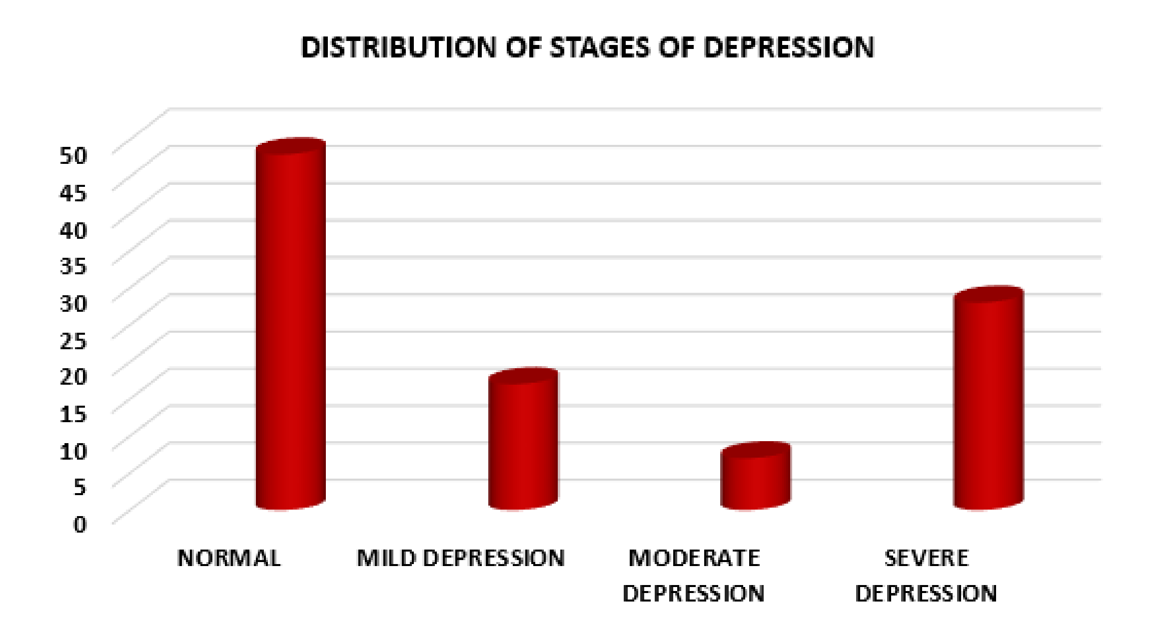


TABLE 17 : DISTRIBUTION OF PATIENTS ACCORDING TO FATIGUE

		FATIGUE	
FATIGUE	NO.(%)	MEAN	S.D.
MILD	42	48.02	1.35
MODERATE	34	38.97	4.06
SEVERE	24	20.75	4.45

Out of the study population , 42% patients had mild fatigue according to FACIT-F scale with a score of 48 ± 1.35 ; 34 % patients had moderate fatigue with a score of 38 ± 4.06 and 24% patients had severe fatigue with a score of 20 ± 4.45.

TABLE 18 : ASSOCIATION BETWEEN BMI AND FATIGUE :

IN THE FOLLOWING TABLE p VALUES ARE OBTAINED USING ONE WAY ANOVA

	FACIT-F														
	MILD (n=42)				MODERATE (n=34)				SEVERE (n=24)						
	MEAN	S.D.	MINIMUM	MAXIMUM	MEAN	S.D.	MINIMUM	MAXIMUM	MEAN	S.D.	MINIMUM	MAXIMUM	F VALUE	p VALUE	INFERENCE
BMI	23.13	3.45	16.6	31.2	22.2452941	2.94	16.7	29.54	19.52	3.50	16.1	29.36	4.8581	0.0098	VS

The mean BMI in mild fatigue was 23 ± 3.45 ; moderate fatigue was 22.24 ±2.94 and severe fatigue was 19.52 ± 3.50. the chi square analysis showed a p value of 0.0038. so there is marked association between BMI and fatigue severity.

	FATIGUE							
	MILD		MODERATE		SEVERE			
BMI	NUMBER(%)	MEAN±SD	NUMBER(%)	%MEAN±SD	NUMBER(%)	MEAN±SD	p VALUE	
<18.5	5(12.1)	17.5±0.7	4(9)	17.3±0.7	12(48)	16.8±0.6	< 0.0046	S
18.5-25	26(63.4)	22.5±1.7	27(81.8)	22.1±1.7	10(44)	20.51±1.5		
25-29.9	9(19.5)	26.7±1.3	3(9)	28.3±1.3	2(8)	18.5±1.2		
>30	2(4.8)	30.7±0.6	0	0.00	0	0.00		

In severe fatigue group 12 patients (48%) were in the underweight group with a mean BMI being 16.8±0.6.so lower BMI is a risk factor for severe fatigue according to this study.

ASSOCIATION BETWEEN SYMPTOMATOLOGY AND FATIGUE :

TABLE 19 : COUGH AND FATIGUE

	FATIGUE								
	MILD		MODERATE		SEVERE				
COUGH	NUMBER	%	NUMBER	%	NUMBER	%	TOTAL	p VALUE	INF
ABSENT	8	61.54	3	23.08	2	15.38	13	0.0001	HS
PRESENT	34	39.08	31	35.63	22	25.29	87		

Cough is the most common symptom experienced by COPD patients. In this study Cough was present in 87% patients. 34% had mild fatigue, 31% had moderate fatigue and severe fatigue was seen in 22% of the patients. The p value of association between cough and fatigue was found to be 0.0001 which is highly significant.

TABLE 20: BREATHLESNESS AND FATIGUE

	FATIGUE								
	MILD		MODERATE		SEVERE				
BREATHLESSNESS	NUMBER	%	NUMBER	%	NUMBER	%	TOTAL	p VALUE	INF
PRESENT	6	46.15	5	38.46	2	15.38	13	0.7368	NS
ABSENT	36	41.38	29	33.33	22	25.29	87		
BREATHLESSNESS AND LEVELS OF FATIGUE ARE INDEPENDENT									

Breathlesness is the second common symptom experienced in this study. Out of the 87 patients moderate fatigue was seen in 36 patients and severe fatigue was seen in 29 patients. There is a marked association found between breathlessness and fatigue severity in this study with a p value of 0.0001

TABLE 21 : ASSOCIATION BETWEEN DURATION OF COPD AND FATIGUE

	FACIT-F														
	MILD (n=42)				MODERATE (n=34)				SEVERE (n=24)						
	MEAN	S.D.	MINIMUM	MAXIMUM	MEAN	S.D.	MINIMUM	MAXIMUM	MEAN	S.D.	MINIMUM	MAXIMUM	F VALUE	p VALUE	INFERENCE
COPD DURATION	5.62	4.84	1	23	9.94	4.16	1	19	19.63	2.93	11	25	84.297	< 0.0001	HS

The mean COPD duration in mild fatigue category was 5.62 ± 4.84 ; moderate fatigue is 9.94 ± 4.16 ; severe category is 19.63 ± 2.93. Thus COPD duration has a linear correlation with the fatigue severity with a p value of <0.0001 which is highly significant.

	FATIGUE							
	MILD		MODERATE		SEVERE			
COPD DURATION	NUMBER(%)	MEAN±SD	NUMBER(%)	%MEAN±SD	NUMBER(%)	MEAN±SD	p VALUE	
<10 YEARS	37(88)	4.0±02.0	15(45.4)	5.6±2.8	1	N	< 0.0001	HS
10-20 YEARS	4(9.5)	15.5±2.8	19(54.5)	12.7±1.4	14(60)	17.82±2.2		
>20 YEARS	1(2.3)	N	N	N	9(40)	22.2±1.1		

In severe fatigue group 9 patients(40%) had COPD duration of >20 years, 14 patients(60%) had a COPD duration of 10-20 years. This table shows as the COPD duration increases the severity of fatigue increases (p=<0.0001).

PEARSON'S COEFFICIENT OF CORRELATION BETWEEN FATIGUE AND COPD DURATION :

FATIGUE ASSOCIATION WITH	r	p VALUE
COPD DURATION	-0.8334	< 0.0001

This table shows a marked association between the COPD duration and fatigue severity (r -0.8334) and p (<0.0001)

TABLE 22 (A) : ASSOCIATION BETWEEN GOLD STAGING AND FATIGUE

IN THE FOLLOWING TABLES p VALUE IS CALCULATEDUSING CHI-SQUARE TEST

	FATIGUE								
	MILD		MODERATE		SEVERE				
GOLD STAGE	NUMBER	%	NUMBER	%	NUMBER	%	TOTAL	p VALUE	INF
MILD	15	83.33	3	16.67	0	0.00	18	<0.0001	HS
MODERATE	22	44.90	24	48.98	3	6.12	49		
SEVERE	4	18.18	7	31.82	11	50.00	22		
VERY SEVERE	1	9.09	0	0.00	10	90.91	11		

THERE IS A HIGHLY SIGNIFICANT ASSOCIATION BEWTEEN GOLD STAGES AND FATIGUE LEVELS

11 out of 22 patients with severe obstruction had severe fatigue level (50%).10 out of 11 patients with very severe obstruction according to GOLD guidelines had severe fatigue (90%).

There was a significant association between COPD severity and the fatigue levels with a p value of <0.0001.

TABLE 22 (B) : ASSOCIATION BETWEEN FEV1 AND FATIGUE

	FACIT-F															
	MILD (n=42)				MODERATE (n=34)				SEVERE (n=24)				OVERALL			
	MEAN	S.D.	MINIMUM	MAXIMUM	MEAN	S.D.	MINIMUM	MAXIMUM	MEAN	S.D.	MINIMUM	MAXIMUM	MEAN	S.D.	MIN	MAX
FEV1	0.69	0.13	0.25	0.84	0.64	0.12	0.37	0.87	0.39	0.14	0.22	0.67	0.60	0.17	0.22	0.87

P value = <0.0001

FEV1 was found to be 0.69 ± 0.13 in mild fatigue patients ; 0.64 ± 0.12 in moderate fatigue and it was 0.60 ± 0.17 in severe fatigue. The chi square test between FEV1 and fatigue severity demonstrates significant association between FEV1 and Fatigue levels with a p value of 0.0001. Hence FEV1 value has significant correlation with Fatigue level.

TABLE 23 : ASSOCIATION BETWEEN LIFESTYLE FACTORS AND FATIGUE

TABLE 23 (A): SMOKING AND FATIGUE

	FATIGUE							
	MILD		MODERATE		SEVERE			
SMOKING INDEX	NUMBER(%)	MEAN±SD	NUMBER(%)	%MEAN±SD	NUMBER(%)	MEAN±SD	p VALUE	
<100	15(68.1)	55.2±19.4	3(15)	70.3±31.6	0	N	< 0.0001	HS
100-200	6(27.7)	137±30.0	8(40)	132.5±23.5	1(4.7)	N		
200-300	0	N	8(40)	245±32.0	8(38)	238.2±22.8		
>300	1(4.5)	N	1(5)	N	12(57.1)	342.3±31.1		

Out of 100 patients included , 63% patients are smokers and rest 37 are non smokers.Patients who had higher smoking index had severe fatigue. In severe fatigue group 12 patients (57%) had Smoking index of >300, 8 patients(38%) had SI of 200-300. There is a linear association between smoking index and severity of the fatigue with a p value of <0.0001 which is highly significant.

TABLE 23 (B) : ALCOHOL AND FATIGUE

	FATIGUE							
	MILD		MODERATE		SEVERE			
ALCOHOL YEARS	NUMBER(%)	MEAN±SD	NUMBER(%)	%MEAN±SD	NUMBER(%)	MEAN±SD	p VALUE	
<10 years	9(40.9)	7.7±0.4	8(42.1)	7.3±1.3	3(15)	7.6±0.5	< 0.0132	NS
10-20 years	11(50)	12.2±1.7	11(57.8)	13.8±1.4	11(55)	14.7±1.6		
20-30 years	2(9)	22.5±0.7	0	N	6(30)	212.1±0.9		
>30 years	0	N	0	N	0	N		

61% Patients gave a history of alcohol intake. There was no significant association between alcohol history and fatigue levels (p=0.7024)

TABLE 24 : ASSOCIATION BETWEEN AGE OF COPD PATIENT AND FATIGUE LEVELS

	FATIGUE								
	MILD		MODERATE		SEVERE				
AGE	NUMBER	%	NUMBER	%	NUMBER	%	TOTAL	p VALUE	INF
40 - 49	7	70.00	3	30.00	0	0.00	10	0.1972	NS
50 - 59	12	46.15	9	34.62	5	19.23	26		
60 - 69	16	43.24	10	27.03	11	29.73	37		
≥ 70	7	25.93	12	44.44	8	29.63	27		
AGE AND LEVELS OF FATIGUE ARE INDEPENDENT									

Among the most common age group (60-69 years), 12 patients had moderate fatigue (27%) and 11 patients had severe fatigue (29.7%). The above table shows that there is no significant association between age of COPD patient and the level of fatigue (p = 0.1972)

TABLE 25 : ASSOCIATION BETWEEN GENDER OF COPD PATIENT AND FATIGUE LEVELS

	FATIGUE								
	MILD		MODERATE		SEVERE				
GENDER	NUMBER	%	NUMBER	%	NUMBER	%	TOTAL	p VALUE	INF
FEMALE	16	55.17	10	34.48	3	10.34	29	0.0879	NS
MALE	26	36.62	24	33.80	21	29.58	71		
GENDER AND LEVELS OF FATIGUE ARE INDEPENDENT									

Majority of the study population are males (71%)

Out of them 26 % patients had mild fatigue , 24 % patients had moderate fatigue and severe fatigue was observed in 21% patients. In the female group, 3% patients had severe fatigue and 10%, had moderate fatigue. However there was no statistically significant association found between the gender and fatigue severity in this study (p=0.0879)

TABLE 26 : ASSOCIATION BETWEEN COMORBIDITIES AND FATIGUE

TABLE 26 (A) ASSOCIATION BETWEEN DIABETES AND FATIGUE :

	FATIGUE								
	MILD		MODERATE		SEVERE				
DIABETES	NUMBER	%	NUMBER	%	NUMBER	%	TOTAL	p VALUE	INF
YES	27	46.50	17	29.31	14	24.13	58	0.3176	NS
NO	15	35.71	17	40.47	10	23.80	42		
TOTAL	42	42.00	34	34.00	24	24.00	100		

Among the 58 diabetic patients 14 patients (24%) had severe fatigue ; 17 had moderate fatigue (14%) and 27 patients had mild fatigue (46%). There is no significant association between fatigue and Diabetes.

TABLE 26 (B) ASSOCOATION BETWEEN HTN AND FATIGUE :

	FATIGUE								
	MILD		MODERATE		SEVERE				
HTN	NUMBER	%	NUMBER	%	NUMBER	%	TOTAL	p VALUE	INF
YES	27	52.94	18	35.29	6	11.76	51	0.0089	VS
NO	15	30.61	16	32.65	18	36.73	49		
TOTAL	42		34		24		100		

Between HTN and fatigue there was a significant association with a p value of 0.0089 which is statistically significant. So hypertension is associated with fatigue.

TABLE 27 : ASSOCIATION BETWEEN FATIGUE AND PAST ADMISSIONS

	FATIGUE							
	MILD		MODERATE		SEVERE			
Past Admission	NUMBER	%	NUMBER	%	NUMBER	%	p VALUE	
0	31	73.80	11	33.30	1	4.00	< 0.0001	HS
1	11	26.10	21	63.60	4	16.00		
2	0	0.00	1	3.00	18	72.00		
3	0	0.00	0	0.00	2	8.00		

In the severe fatigue group, 18 patients(72%) had 2 admissions and 2 patients(8%) had 3 admissions and 4 patients (16%) had 1 admission in the past year .This table shows there is a significant relationship between past admission and fatigue severity with a p value of 0.0001

TABLE 28 : ASSOCIATION BETWEEN FATIGUE AND MMRC

	FATIGUE								
	MILD		MODERATE		SEVERE				
MMRC	NUMBER	%	NUMBER	%	NUMBER	%	TOTAL	p VALUE	INF
0	10	76.92	3	23.08	0	0.00	13	< 0.0001	HS
1	20	57.14	14	40.00	1	2.86	35		
2	11	29.73	16	43.24	10	27.03	37		
3	1	6.67	1	6.67	13	86.67	15		
LEVELS OF MMRC ARE HIGHLY ASSOCIATED WITH LEVELS OF FATIGUE									

Among the 37 patients with MMRC grade 2 , 10 patients (27%) had severe fatigue ; 16 patients had moderate fatigue (43%). In MMRC grade 3 patients (Total -15) 13 of them had severe fatigue (86%) . According to this table there is a linear relationship between MMRC grading and the severity of fatigue. The chi square comparison of these two variable yielded a p value of 0.0001 which is statistically significant.

TABLE 29 : FATIGUE AND 6MWD ASSOCIATION

	MILD				MODERATE				SEVERE				OVERALL			
	MEAN	S.D.	MIN	MAX	MEAN	S.D.	MIN	MAX	MEAN	S.D.	MIN	MAX	MEAN	S.D.	MIN	MAX
6MWD	374.10	87.68	30	462	350.24	74.35	145	456	214.20	78.37	120	349	326.25	103.89	30	462

The patients in the milder fatigue group had covered a 6MWD(distance) of 374 ±87.6 metres ; moderate group had 350.24 ± 74.35 metres and severe fatigue group had 214 ± 78.37 metres . Thus there is a decrease in the mean 6MWD as the severity increases which shows a relationship between the 6MWD and the fatigue severity.

Pearson correlation between fatigue and 6MWD

WITH	r	p VALUE
6MWD	0.6562	< 0.0001

The pearson coefficient analysis between the variables showed a p value of 0.0001 demonstrating a strong association between 6MWD and fatigue severity**.**

TABLE 30 : ASSOCIATION BETWEEN FATIGUE AND DEPRESSION

	FATIGUE								
	MILD		MODERATE		SEVERE				
DEPRESSION	NUMBER	%	NUMBER	%	NUMBER	%	TOTAL	p VALUE	INF
NORMAL	35	72.92	12	25.00	1	2.08	48	< 0.0001	HS
MILD	3	17.65	13	76.47	1	5.88	17		
MODERATE	1	14.29	6	85.71	0	0.00	7		
SEVERE	3	10.71	3	10.71	22	78.57	28		
THERE IS A HIGHLY SIGNIFICANT ASSOCIATION BEWTEEN DEPRESSION AND FATIGUE LEVELS									

Out of the 28 patients who suffered from severe depression according to the CES-D scale, 22 had severe depression (78%) 1 patient (5%) had moderate depression.

In the moderate fatigue group, 3 patients (10%) had severe depression and 6 patients (85%) had moderate and 13(76%) had mild depression.

In the mild fatigue group, 3 patients (10%) had severe, 1 patient had moderate and 35 patients (72%) had no depression at al.

The chi-square analysis between the Fatigue severity and the level of depression with a p value of <0.0001 which is statistically significant.

So according to this study Depression is a major risk factor for fatigue.

TABLE 31 : ASSOCIATION BETWEEN FATIGUE AND HEALTH STATUS (SGRQ)

IN THE FOLLOWING TABLE p VALUES ARE OBTAINED USING ONE WAY ANOVA

		FACIT-F														
		MILD (n=42)				MODERATE (n=34)				SEVERE (n=24)						
		MEAN	S.D.	MINIMUM	MAXIMUM	MEAN	S.D.	MINIMUM	MAXIMUM	MEAN	S.D.	MINIMUM	MAXIMUM	F VALUE	p VALUE	INFERENCE
SGRQ	SYMPTOM	20.71	12.75	5.23	60.81	29.14	13.65	5.34	55.56	55.31	11.92	5.76	66.95	56.2804	< 0.0001	HS
	ACTIVITY	22.29	25.21	7.82	157.32	29.12	16.91	4.87	59.24	56.72	7.32	36.75	64.58	24.8654	< 0.0001	HS
	IMPACT	8.25	3.86	4.72	19.47	11.84	4.99	6.28	20.34	19.37	2.08	14.8	22.84	59.9025	< 0.0001	HS
	TOTAL	17.09	11.67	8.42	60.39	23.37	11.14	9.92	42.35	43.80	5.55	27.57	51.46	52.0967	< 0.0001	HS

The SGRQ symptom score in severe group was 55.31 ± 11.92 ; moderate group was 29.14 ± 13.65 and mild group was 20.71 ± 12.75. Similarly the other domains of the SGRQ questionnaire which attributes to the physical, psycho-social symptoms also showed association with the fatigue severity. The chi square analysis showed a p value of <0.0001.

So according to this study fatigue has an impact on the Health related quality of life of the COPD patients.

DISCUSSION:

COPD is a major cause of disability and death worldwide. In contrast to the significant decline in morbidity and mortality observed with other chronic diseases, the issues with COPD is constantly increasing.

The overall prevalence of the fatigue in general population is 18.3% -25%. However in COPD it is “almost always experienced by 43%-72% of the population[96]. Fatigue is a common distressing symptom of this disease. It significanty impairs the quality of life and the patients functional performance. Fatigue imposes limitations on motivation, concentration and the ability to engage in everyday ctivities such as work , household chores and social past times , depression , grief and a sense of loss of control [65,97].

A total of 100 stable COPD patients were included in this study. Clinical examination , PFT , answering questionnaires (CES-D, SGRQ , FACIT-F) and 6MWT was done on the same day in the same order.

Most of the patients were in the age group of 60-70 years. Mean age of the population was 65.49 ± 5.87 years. The higher study age group is similar and comparable to the mean age in other studies [78,80,98]. There is no significant correlation between fatigue and age according to this study. This finding is concurrent with few other studies done by Baghai-Ravary and colleagues [73] and Lewko and colleagues [80] which stated that Fatigue in COPD is independent of the age and elderly patients with COPD experience more fatigue than their age matched colleague without COPD.

There were 81 males and 19 females in our study, with a male predominance. There is no substantial relation found between gender and the incidence of fatigue in the study population. A study done by Theander and colleagues [81] using the Fatigue Impact scale in

345 COPD patients revealed a similar inference that there were no significant difference in fatigue between COPD men and women as opposed to the healthy subjects.

Out of the 81 males, smoking history was seen in 63 males, and smoking history was not seen with the female population. There are several studies which illustrate the high prevalence of COPD among the male population in India [75]. This can be attributed to the higher predominance of smoking habit in Indian males as compared to the females.

This study showed that occurrence of fatigue in COPD is more in the smoking population compared to the non- smoking population (with a p value of 0.0314) which is statistically significant. The severity of fatigue also correlates with the smoking index of the patient.In the severe fatigue group, 57% patients had smoking index of >200 and 38% had SI >300.

This is keeping with the results obtained by kentson and colleagues[99] who has done a study in 107 COPD patients which demonstrated that smoking has a negative impact on both physical and cognitive dimension of the FIS (Fatigue Impact Scale).Goertz and colleagues also has proved that fatigue severity has significant correlation with Pack years smoking history pack years ($r_s = 0.129$, $p = 0.073$).

The average duration of COPD in the study population was 11.63 ± 3.87 years. 37% of patient had the disease duration between 10-20 years. This study had shown marked relation between the disease duration and the level of fatigue with a p value of < 0.0001 which is statistically significant. A study done by Peters et al[75] which included 168 stable COPD patients demonstrated similar result. When the patient were followed up after a period of 4 years, the fatigue level increased from 45.5% to 63.7% .

Spirometry assessment was made with post broncho dilator FEV1, FEV1/FVC at the baseline. FEV1 (Forced expiratory volume over 1 second is a dynamic measure of flow. It measures the true obstruction of airflow and also an indicator of airflow obstruction severity. Out of 100 patients 49 of them had moderate obstruction, 22 of them severe and 11 very severe obstruction. 90% of the patients with very severe obstruction had severe fatigue as compared to 50% of them with severe obstruction. There is a linear relationship between the severity of COPD (GOLD stage) with the level of fatigue with a p value of <0.0001.

This is keeping with the results obtained by Kristina and colleagues[100] and Deniz and colleagues who found a relationship between fatigue level and FEV1.

The mean FEV1 in the milder group population was 0.69 ± 0.13 and in the moderate fatigue group it was found to be 0.64 ± 0.12. In the severe fatigue group the FEV1 was 0.39±0.34.

In this study population most of them (50%) of the patient were in the normal BMI range (18.5-24.5). These 50 patients had a FACIT-F score of 40.22 ± 9.14 . Twenty six patients were in the underweight group with a FACIT-F score being 30.26 ± 13.24 . Patients in the severe fatigue group had a lesser mean BMI (19.52) when compared to the moderate fatigue (mean BMI-22.24) and mild fatigue group (mean BMI-23.13). with a p value of 0.0001(very significant). Hence according to this study , severity of fatigue perceived is more in patients with lower BMI as compared with people with normal BMI or overweight. This is due to the poor nutritional status , muscle wasting and reduced exercise capacity leading to fatigue.

A study done by Huber and colleagues[101] in 11,577 patients. This study found out that lower BMI is associated with higher incidence of emphysema. Emphysema corresponds to lower HrQOL and is usually seen in people with grade 4 COPD.

Among the 100 patients 85 had history of hospital admission in the past year. Out of these 85 patients , 32 of the patients (37.65%) had moderate level of fatigue ,24 patients (28.24%) had severe fatigue and 29 patients (34.12%) had mild fatigue. When Karl pearson co efficient was used to calculate the correlation between the level of fatigue and hospital admission, the r value was found to be -0.5179 with a p value of <0.0001 which is statistically significant. Hence according to this study history of past admission has significant association with the level of fatigue in COPD patients. A study done by Goertz and colleagues[102] in 1290 patients demonstrated that patients who experienced severe fatigue had experienced more exacerbations in the last 12 months.

Another study done by Padisson and colleagues[8] on 100 COPD patients showed that those reporting the most intense scores on fatigue impacts showed a 13.6-fold increase in risk of hospitalisation (95% CI 2.50–74.20).

Our study had showed that there is a correlation between co-morbidity and fatigue. Hypertension has been associated with marked occurrence of fatigue, although no relation was revealed between Diabetes and Fatigue. A similar study by Goertz and colleagues[102] on 1290 patient showed that one of the factors that correlate with fatigue in COPD patients was associated comorbidities.

Fatigue severity directly correlated with the level of dyspnea experienced by the patient was one of the finding of this study. Reihstein and colleagues[103] observed a correlation between fatigue and dyspnea of a moderate magnitude ($r = 0.43$), similar to this study. Gift and Shepard[104] ($r = 0.63$), Woo and colleagues[105] ($r = 0.69$), Kapella and

colleagues[106] ($r = 0.74$) and Kinsman and colleagues[107] ($r = 0.76$) found a similar correlation of a between fatigue and dyspnea which is of great significance.

Of the patients found with severe depression in this study, most of them had severe fatigue (22 of 28 i.e 78%).our study showed that thus severe fatigue can lead to depression and vice-versa.

Kentson et al[98] did a similar study on 101 COPD patients which demonstrated that experience of fatigue was associated with depression [odds ratio (OR) 1.69, 95% confidence interval (CI) 1.28–2.25). Fatigue was more common in patients with COPD than in control patients (72% versus 56%, $p < 0.001$). Patients with COPD and fatigue had lower lung function, shorter 6MWD, more dyspnoea, anxiety and depressive symptoms, and worse health status compared with patients without fatigue ($p < 0.01$). Multiple logistic regression analysis showed that depression was independently associated with fatigue, with ORs (95% CI) of 1.69 (1.28–2.25), $p < 0.001$ for depression.

Fatigue is associated with reduced functional health status and quality of life impairing the patients , physical ,psychosocial and cognitive capabilities. wong and colleagues[108] did a study in 43 pulmonary rehabilitation participants which revealed experience of fatigue is associated with dimensions of reduced activity (88.1%), reduced motivation (83.3%), mental fatigue (69.9%), and general fatigue (54.5%).

The study has a strength that it mainly involves finding out the factors that determines the onset of fatigue and the Impact it has on different dimensions of the patients life like Physical ,psychological, cognitive aspects of the patient rather than concentrating one particular domain. The study involves subjective questionnairres , so it eliminates bias.

LIMTATIONS:

The major limitation of the study is that, it is a single centre study. Another drawback is that the sample size is small , although it is comparable to other similar studies done in this aspect.

CONCLUSION :

Duration of COPD , severity of the disease according to GOLD criteria , FEV1, presence of comorbiditied , Low BMI, past admission history, smoking are all important determinants of Fatigue in a COPD patient.

Moderate to severe fatigue will have an effect on patients degree of breathlessness, exercise capacity , and other physical and psycho-social domains of the patients life with reduction in the quality of life. Significant fatigue may also lead to Depression in a COPD patient and Vice-Versa.

SUMMARY:

- A total of 100 stable COPD patients were included in this study with majority being male population(81 Males and 19 females)
- Most of the study population were in the age group 60-70 years age
- A vast majority of the patients were smokers.i.e 63% of study population.
- Demographic data, clinical examination,PFT,6MWT and oral questionnaires regarding CES-D,SGRQ and FACTI-F were taken in the same day.
- BMI, obstruction of airways (FEV1) by PFT, breathlessness by MMRC and exercise capacity by 6MWT were assessed.
- Smoking had significant co-relation with severity of the fatigue. Patients with higher smoking index had higher levels of fatigue which was statistically significant.
- Age and gender did not have any correlation with fatigue severity.
- COPD duration, FEV1, previous hospitalization, BMI, co-morbidity (HTN),GOLD staging had a significant impact on the level of fatigue.
- The severity of fatigue was found to have major impact on the patient's level of dyspnoea (MMRC) , excercise capacity (6MWT), and quality of life and health status as assessed by SGRQ.
- The presence of fatigue also is a determining factor for the presence of depression in COPD patients. The fatigue severity has been found to have a significant correlation with the severity of depression.

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ANNEXURE – 1

INFORMED CONSENT

TITLE OF THE STUDY: "DETERMINANTS AND IMPACT OF FATIGUE IN COPD-A ONE YEAR HOSPITAL BASED CROSS SECTIONAL STUDY"

INTRODUCTION AND PURPOSE:

The purpose of this study is to evaluate the determinants and impacts of fatigue in COPD. Fatigue is the second common symptom in COPD next to breathlesness. Fatigue can have a significant impact in the quality of daily life in COPD patients. Clinically significant fatigue can can cause increased disease burden and can affect patients physical, mental and social life.

This study aids in finding out the Determinants and impact of fatigue in COPD and therby serves as a tool to avoid the factors that lead to fatigue in patients of COPD.

PROCEDURE:

I request you to kindly participate in the study titled **"DETERMINANTS AND IMPACT OF FATIGUE IN COPD-A ONE YEAR HOSPITAL BASED CROSS SECTIONAL STUDY"** at Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi is being conducted by Post graduate in Respiratory Medicine at J.N. Medical College Belagavi, Karnataka.

We request you to participate in this study as you are eligible to be included. During the study, you will be asked questions regarding your present and past medical history and you will be required to answer to the best of your knowledge. You will also be clinically examined as per the protocol drawn.

If you agree to participate in the study, please furnish the details pertaining to the study.

BENEFITS:

- Finding out the factors that cause fatigue and its effect in the severity of the disease in COPD patients

COMPLICATIONS: NIL

ALTERNATIVES:

If you are not willing to take part in the study, your treatment or any other further investigations the patient wants to undergo, in future, in KLE will not be affected by your decision.

VOLUNTARY PARTICIPATION/WITHDRAWAL:

Taking part in this study is voluntary. You may choose not to take part in this study, or if you decide to take part, you can later change my mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor or the sponsor may stop your participation in this study. You will tell if any important new findings that may change my willingness to continue to take part. If you choose not to take part in the study, you will receive the standard treatment for patients with your condition.

COSTS: NIL

Payment for Participation: No incentive will be paid to you for participating in this study.

COMPENSATION:

In the event that you become injured as a result of taking part in this study, treatment whatever available at KLE Charitable hospital, Belagavi, will be offered to you. No reimbursement, compensation or free medical care is given.

CONFIDENTIALITY:

All information collected about you during the course of the study will be kept confidential to the extent permitted by the law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be kept confidential in any publication/ presentation.

Compensation :

In the event of any adverse effect related to the study, treatment will be made available through KLES Hospital and MRC, Belgaum. There is no compensation or payment for such medical treatment by law. For any further queries you may contact PG in Department of Respiratory Medicine.

Authorization to publish results :

The results of this study would be forwarded to KLE Academy of Higher Education, Belgaum as a part of requirement towards the completion of MD degree, review and publishing.

QUESTION: If you have any enquiries in the future or in case of research related injury illness, you may contact following persons.

Post-Graduate, Department of Respiratory Medicine J.N.Medical College, Belagavi.	Guide, Professor Department of Respiratory Medicine, J.N.Medical College, Belagavi.	Professor, Chairman, J.N. Medical College Institutional Ethical Committee for Human Subjects Research.

CONSENT TO PARTICIPATE IN RESEARCH STUDY:

1. "I understand that I am participating in the study,that involves answering questions about my general health conditions, doing spirometry test, general physical examination,and a 6 minute walk test(6MWT).
2. I confirm that I have read and understood the information in the patient information sheet. Procedure is explained to me in detail along with information about the advantages and disadvantages of taking part in the study. I have been given the opportunity to discuss all aspects of the trial, to ask questions and hereby consent to participation in the trial outlined above.
3. I understand that the decision to take part in this study is completely voluntary and I am aware that I can choose to withdraw from the study at any point of time.
4. I understand that there is no significant risk involved in the test that would be done in this study.
5. No guarantee or assurance has given by anyone as to the results that may be obtained.
6. My signature on this form signifies that I have willingly decided to participate after understanding the above information".

Participant's Name/ legally authorized _______________________

Representative Signature / left thumb impression _______________________

Name and signature / left thumb impression of witness _______________________

Name and signature of interviewer Date:

____

Place_____________

Address:_____________

ANNEXURE II- PROFORMA

Name :

Age :

Sex :

Occupation :

Chief complaints :

Cough / Breathlessness / Chest pain / Pain abdomen

Other symptoms :

MMRC grading of breathlessness :

Past history :

- K/C/O COPD for _________ years
- No.of Hospitalizations :
- History of Diabetes Mellitus / Hypertension / Asthma / Tuberculosis
- Other Comorbidities

Personal History :

Smoking / Alcohol / Tobacco chewer

General Physical Examination

Height : Weight : BMI :

Pulse rate : BP : RR :
SpO_2 :

Pallor / Icterus / Cyanosis / Clubbing / Pedal edema / Lymphadenopathy / Koilonychia

Systemic Examination

Respiratory System :

Other Systems :

PFT

FEV_1 / FVC :

FEV_1% predicted :

FVC % predicted :

6MWD :

SGRQ

PART 1

1) Over the last year, I have coughed:
Most 80.6
Several 63.2
A few 29.3
Only 28.1
Not 0.0

2) Over the last year, I have brought up phlegm (sputum):
Most 76.8
Several 60.0
A few 34.0
Only 30.2
Not 0.0

3) Over the last year, I have had shortness of breath:
Most 87.2
Several 71.4
A few 43.7
Only 35.7
Not 0.0

4) Over the last year, I have had attacks of wheezing:
Most 86.2
Several 71.0
A few 45.6
Only 36.4
Not 0.0

5) During the last year, how many severe or very bad unpleasant attacks of chest trouble have you had?
More than three 86.7
3 attacks 73.5
2 attacks 60.3
1 attack 44.2
None 0.0

6) How long did the worst attack of chest trouble last?
a week or more 89.7
3 or more days 73.5
1 or 2 days 58.8
less than a day 41.9

7) Over the last year, in an average week, how many good days (with little chest trouble) have you had?
None 93.3
1 or 2 76.6
3 or 4 61.5
nearly every day 15.4
every day 0.0

8) If you have a wheeze, is it worse in the morning?

No 0.0
Yes 62.0

PART 2

9) How would you describe your chest condition?

The most important problem I have 83 .2

Causes me quite a lot of problems 82.5

Causes me a few problems 34.6

Causes no problem 0.0

10) If you have ever had paid employment?

My chest trouble made me stop work 88.9

My chest trouble interferes with my work or made me change my work 77.6

My chest trouble does not affect my work 0.0

11) Questions about what activities usually make you feel breathless.

Sitting or lying still 90.6

Getting washed or dressed 82.8

Walking around the home 80.2

Walking outside on the level 81.4

Walking up a flight of stairs 76.1

Walking up hills 75.1

Playing sports or games 72.1

12) More questions about your cough and breathlessness.

My cough hurts 81.1

My cough makes me tired 79.1

I get breathless when I talk 84.5

I get breathless when I bend over 76.8

My cough or breathing disturbs my sleep 87.9

I get exhausted easily 84.0

13) Questions about other effects your chest trouble may have on you.

My cough or breathing is embarrassing in public 74.1

My chest trouble is a nuisance to my family, friends or neighbours 79.1

I get afraid or panic when I cannot get my breath 87.7

I feel that I am not in control of my chest problem 90.1

I do not expect my chest to get any better 82.3

I have become frail or an invalid because of my chest 89.9

Exercise is not safe for me 75.7

Everything seems too much of an effort 84.5

14) Questions about your medication.

My medication does not help me very much 88.2

I get embarrassed using my medication in public 53.9

I have unpleasant side effects from my medication 81.1

My medication interferes with my life a lot 70.3

15) Questions about how activities may be affected by your breathing.

I take a long time to get washed or dressed 74.2

I cannot take a bath or shower, or I take a long time 81.0

I walk more slowly than other people, or I stop for rests 71.7

Jobs such as housework take a long time, or I have to stop for rests 70.6

If I walk up one flight of stairs, I have to go slowly or stop 71.6

If I hurry or walk fast, I have to stop or slow down 72.3

My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, play bowls or play golf 74.5

My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim 71.4

My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports 63.5

16) We would like to know how your chest trouble usually affects your daily life.

I cannot play sports or games 64.8

I cannot go out for entertainment or recreation 79.8

I cannot go out of the house to do the shopping 81.0

I cannot do housework 79.1

I cannot move far from my bed or chair 94.0

17) Tick the statement which you think best describes how your chest affects you.

It does not stop me doing anything I would like to do 0.0 It stops me doing one or two things I would like to do 42.0

It stops me doing most of the things I would like to do 84.2

It stops me doing everything I would like to do 96.7

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Center for Epidemiologic Studies Depression Scale (CES-D), NIMH

Below is a list of the ways you might have felt or behaved. Please tell me how often you have felt this way during the past week.

	During the Past Week			
	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	Most or all of the time (5-7 days)
1. I was bothered by things that usually don't bother me.	☐	☐	☐	☐
2. I did not feel like eating; my appetite was poor.	☐	☐	☐	☐
3. I felt that I could not shake off the blues even with help from my family or friends.	☐	☐	☐	☐
4. I felt I was just as good as other people.	☐	☐	☐	☐
5. I had trouble keeping my mind on what I was doing.	☐	☐	☐	☐
6. I felt depressed.	☐	☐	☐	☐
7. I felt that everything I did was an effort.	☐	☐	☐	☐
8. I felt hopeful about the future.	☐	☐	☐	☐
9. I thought my life had been a failure.	☐	☐	☐	☐
10. I felt fearful.	☐	☐	☐	☐
11. My sleep was restless.	☐	☐	☐	☐
12. I was happy.	☐	☐	☐	☐
13. I talked less than usual.	☐	☐	☐	☐
14. I felt lonely.	☐	☐	☐	☐
15. People were unfriendly.	☐	☐	☐	☐
16. I enjoyed life.	☐	☐	☐	☐
17. I had crying spells.	☐	☐	☐	☐
18. I felt sad.	☐	☐	☐	☐
19. I felt that people dislike me.	☐	☐	☐	☐
20. I could not get "going."	☐	☐	☐	☐

SCORING: zero for answers in the first column, 1 for answers in the second column, 2 for answers in the third column, 3 for answers in the fourth column. The scoring of positive items is reversed. Possible range of scores is zero to 60, with the higher scores indicating the presence of more symptomatology.

ANNEXURE -3 – ETHICAL CLEARANCE LETTER

K.L.E. ACADEMY OF HIGHER EDUCATION AND RESEARCH
(Deemed - to - be - University)
Accredited 'A' Grade by NAAC (2nd Cycle) Placed in Category 'A' by MHRD (GoI)

JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)

Website: http//www.jnmc.edu
E-Mail : dome@jnmc.edu

Phone: (+ 91-(0)831 Office : 2472550
Principal: 2471701
Fax No. +91 (0)831 - 2470759

Ref: MDC/DOME/ 233 **Date: 24/12/2019**

To,
BR0119003
PG student in Respiratory Medicine,
J.N.Medical College,
BELAGAVI.

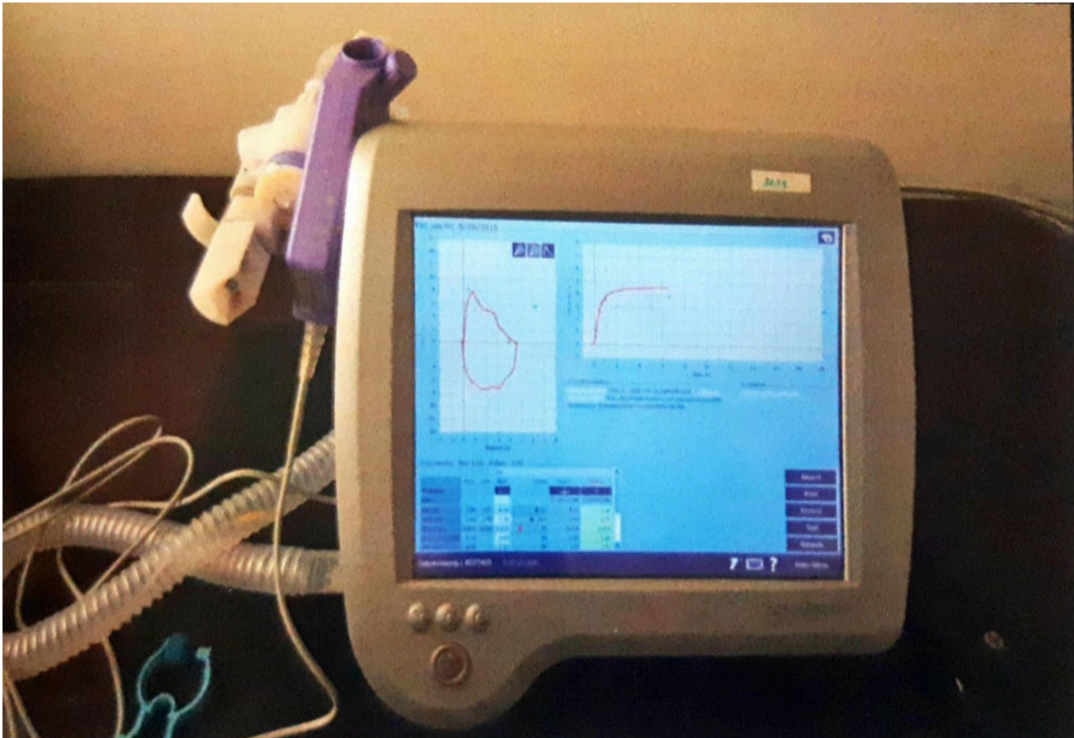
Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"DETERMINANTS AND IMPACT OF FATIGUE IN COPD-A ONE YEAR HOSPITAL BASED CROSS SECTIONAL STUDY"**, is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Anita Dalal)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

(Dr. Roopa M Bellad)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

ANNEXURE -4 PHOTGRAPHS



SPIROMETER

ANNEXURE – 5 KEY TO MASTER CHART

6MWD – 6 Minute Walk Distance

BMI – Body Mass Index

CES-D – Centre for Epidemiological Studies Depression scale

SGRQ -- St. George Respiratory Questionnaire

MMRC -- Modified Medical research Council Scale

FACIT -- Functional Assessment of Chronic Ilness Therapy

ANNEXURE – 6 MASTER CHART

PATIENT NO.	AGE	SEX	BMI	COUGH	BREATHLE:	COPD DUR	GOLD STA(	SMOKING	SMOKING	SMOKING	ALCOHOL	COHOL YEA	ST ADMISSI	DIABETES	HTN	IHD	FEV1	FEV1/FVC	6MWD	MMRC	CES D	FACIT-F	RQ-SYMPT(	SGRQ-ACT	SGRQ-IMPACT
1044814	65	M	21.44	Y	Y	13	1	Y	8	96	Y	13	1	Y	N	N	80%	0.638	431	1	12	46	23.12	14.12	7.68
1045530	61	M	22.34	Y	Y	7	2	N			N	8	1	Y	N	N	72%	0.82	412	1	17	38	23.56	14.67	8.68
1046299	61	M	24.56	Y	N	12	2	Y	15	270	N	12	1	N	N	N	67%	0.63	360	1	18	38	24.02	22.56	6.82
1046710	73	M	19.21	Y	Y	14	2	Y	14	210	Y	17	1	Y	Y	N	64%	O.71	340	2	33	36	45.2	43.5	15.2
1046730	50	F	31.2	N	Y	5	2	N			N	N	0	Y	N	N	66%	0.52	282	2	18	48	22.05	17.2	12.65
1047793	65	F	17.34	Y	Y	7	2	N			N	N	0	Y	N	N	72%	0.76	30	2	19	47	20.48	20.45	14.56
1047855	74	M	20.75	Y	Y	23	4	Y	21	420	Y	23	1	Y	N	Y	25%	0.3	163	3	45	50	5.23	52.56	16.78
1047232	56	F	23.98	Y	Y	5	2	N			N	N	0	N	N	N	76%	0.77	440	1	12	49	18.25	15.32	7.26
6034585	61	F	24. 21	Y	Y	3	2	N			N	N	0	Y	N	N	76%	0.79	462	1	13	50	18.52	157.32	5.32
6034396	57	M	24.5	Y	Y	13	2	Y	13	130	Y	8	1	N	Y	Y	62%	0.61	310	2	24	48	60.23	55.46	17.23
6020913	56	F	19.45	Y	Y	6	2	N	12	96	N	N	1	Y	N	N	74%	0.72	423	1	15	48	16.24	14.23	7.23
1043605	68	M	16.87	N	Y	18	4	Y	23	320	Y	13	2	N	N	N	24%	0.36	143	3	52	22	58.58	60.21	18.32
1043186	60	M	21.22	Y	Y	7	2	N			Y	14	0	Y	N	N	76%	0.68	460	1	19	46	55.23	48.34	16.23
1043178	69	M	23.56	y	y	13	3	N			Y	14	0	y	y	N	48%	0.58	310	2	22	42	45.52	50.23	16.67
1042753	63	M	29.54	Y	Y	13	2	Y	14	140	Y	15	1	N	Y	Y	63%	0.59	289	2	17	43	22.05	16.25	9.23
1042870	55	M	28.23	Y	Y	5	2	Y	7	42	N	8	0	N	Y	N	76%	0.45	436	0	10	48	13.25	9.23	7.17
1042512	70	F	22.13	y	y	20	3	N			N	N	2	Y	Y	N	47%	0.51	145	3	55	21	56.67	62.58	20.25
1040858	57	M	17.3	Y	Y	5	2	Y	8	64	Y	12	0	Y	N	N	67%	0.63	379	1	11	48	17.9	13.25	6.78
1040132	62	F	20.3	N	Y	8	2	N			N	N	0	N	Y	N	73%	0.72	456	1	14	43	17.28	17.26	8.83
1039665	77	M	20.25	Y	Y	19	3	Y	24	240	Y	16	2	Y	Y	N	50%	0.42	258	2	47	18	5.34	59.24	18.37
5981762	69	M	21.22	Y	Y	12	2	Y	16	260	Y	13	1	Y	N	N	68%	0.71	412	2	23	43	48.34	58.36	20.34
103963	60	M	19.44	Y	Y	11	2	N			N	N	0	N	N	N	72%	0.73	434	1	18	44	22.53	14.32	6.98
1038656	70	M	16.23	Y	Y	17	3	Y	22	308	Y	20	2	Y	Y	N	48%	0.52	316	2	32	28	47.34	54.43	15.23
1038169	63	M	21.9	Y	Y	6	2	Y	8	48	N	N	0	Y	Y	N	58%	0.67	290	1	8	48	14.27	11.23	5.28
1036584	60	M	16.6	Y	Y	7	2	Y	12	168	Y	7	1	N	N	N	65%	0.75	380	2	14	48	15.24	14.82	6.73
1037728	50	M	18.3	Y	Y	4	1	Y	6	60	Y	8	0	Y	N	N	82%	0.72	420	0	10	50	12.25	8.93	5.27
1037580	71	M	21.2	Y	Y	18	3	Y	13	104	Y	22	1	Y	Y	N	45%	0.52	320	2	45	48	60.81	59.53	19.47
1036826	49	M	24.6	Y	Y	2	1	Y	5	50	N	N	0	N	Y	N	82%	0.72	450	0	4	50	18.28	13.3	7.38
1037012	60	F	19.5	Y	Y	8	2	N			N	N	0	Y	N	N	65%	0.57	330	1	15	50	22.04	16.72	8.69
1033490	50	M	25.1	Y	Y	4	1	Y	7	48	Y	8	0	Y	Y	N	82%	0.72	396	1	13	47	18.35	16.28	6.25
4366333	63	F	19.4	Y	Y	6	2	N			N	N	0	Y	Y	N	61%	0.54	385	1	12	46	19.42	17.98	7.21
1031808	66	M	22.2	Y	N	7	2	Y	14	280	N	5	1	Y	N	N	58%	0.63	340	2	14	43	17.45	14.58	6.3
1029930	72	M	22.86	Y	N	20	4	Y	24	360	N	22	2	Y	Y	Y	22%	0.35	219	3	52	15	66.35	61.82	21.84
1027424	70	M	29.36	Y	Y	17	2	Y	23	230	N	15	2	Y	N	N	67%	0.58	247	2	49	22	55.84	63.92	20.49
1018855	62	F	17.2	Y	Y	12	2	N			N	N	0	Y	N	N	57%	0.51	261	2	17	38	48.25	55.76	16.32
1026457	65	F	22.1	Y	Y	9	2	N			N	N	0	N	Y	N	69%	0.62	369	1	15	44	18.27	17.83	9.54
1026474	66	M	21.8	Y	Y	12	2	Y	7	35	Y	8	0	Y	N	Y	63%	0.69	345	2	27	43	38.65	44.76	16.54
1025793	74	M	19.17	Y	Y	23	4	Y	22	220	N	12	3	N	N	Y	27%	0.33	175	3	55	14	60.54	58.85	19.05
1024699	60	F	22.6	Y	Y	7	2	N			N	N	0	Y	N	N	71%	0.69	420	0	12	46	18.71	13.48	6.94
5765311	62	M	19.2	Y	Y	11	2	Y	10	200	Y	9	1	Y	Y	N	51%	0.56	367	2	22	39	55.56	48.85	17.83
1018532	71	M	20.3	Y	Y	22	3	Y	25	325	Y	16	2	Y	Y	Y	45%	0.51	148	3	55	18	60.54	60.56	18.75
246666	72	M	19.3	Y	Y	18	2	Y	22	320	Y	15	2	Y	Y	N	59%	0.63	328	2	48	26	55.78	62.56	19.54
1017378	74	M	19.4	Y	Y	19	3	Y	18	369	Y	21	2	Y	Y	Y	45%	0.54	310	2	52	26	63.76	59.43	22.65
1013685	57	M	27.65	Y	N	7	3	Y	7	42	N	12	0	Y	N	N	47%	0.51	280	2	14	48	22.45	17.73	6.85
1014983	51	F	23.6	Y	Y	3	2	N			N	N	1	Y	N	N	67%	0.73	410	1	7	49	12.34	14.45	5.46
1013198	60	F	26	Y	Y	5	2	N			N	N	0	Y	N	N	59%	0.65	267	2	12	48	14.92	12.29	5.29
1013432	70	F	17.2	Y	Y	21	4	N			N	N	2	Y	Y	N	28%	0.41	132	3	49	18	60.46	58.29	21.72
1012043	68	M	27.65	Y	Y	16	3	Y	22	396	Y	8	1	Y	N	Y	45%	0.51	305	2	27	22	56.38	62.29	20.29
3031363	52	F	21.3	Y	Y	3	1	N			N	N	0	Y	N	N	68%	0.61	410	1	10	49	17.38	14.28	6.2
5661546	72	M	18.3	Y	Y	21	3	Y	23	260	Y	22	2	Y	Y	Y	44%	0.56	161	3	52	23	56.76	60.38	20.65
1456727	50	F	22	Y	Y	2	1	N			N	N	0	Y	N	N	81%	0.79	410	1	8	50	17.43	14.87	6.98
1006040	66	M	22.4	Y	Y	15	2	Y	14	168	Y	12	1	Y	Y	N	58%	0.66	245	2	23	33	48.65	45.98	16.76
5634974	72	M	19.2	Y	Y	22	4	Y	18	260	Y	15	2	Y	Y	N	27%	0.32	132	3	54	23	60.65	59.75	16.47
104877	77	M	24.2	Y	Y	16	3	Y	12	96	N	13	1	Y	N	N	47%	0.41	320	2	17	33	38.76	36.87	15.39
1425610	62	M	24.65	Y	Y	12	2	Y	15	220	N	8	1	N	N	N	68%	0.52	349	1	19	40	48.85	50.76	16.58
5627056	51	M	24.4	Y	Y	4	1	Y	5	25	Y	7	0	Y	N	N	72%	0.69	410	1	8	48	15.65	10.76	4.76
1000346	70	F	19.17	N	Y	20	3	N			N	N	0	Y	Y	N	47%	0.65	286	2	50	19	55.04	48.26	20.72
1438370	50	M	22.12	Y	Y	7	2	N			N	N	0	Y	Y	N	72%	0.69	412	1	13	43	17.65	14.71	6.79
5714132	65	M	22.2	Y	Y	18	3	Y	18	270	N	7	2	Y	Y	N	45%	0.51	154	3	48	27	55.28	39.74	18.3
5731824	64	F	24.5	N	Y	8	2	Y	12	120	Y	14	1	Y	N	N	67%	0.71	401	1	15	37	18.76	14.23	6.96
4959572	70	M	21.4	Y	Y	14	3	Y	18	340	N	13	2	Y	N	Y	45%	0.56	145	2	17	33	19.56	16.29	7.3
57297513	45	M	30.3	Y	Y	3	2	Y	6	42	Y	8	0	Y	Y	N	65%	0.61	316	2	5	48	15.27	9.39	6.32
5057970	43	M	25	N	Y	1	1	N			N	N	0	N	N	N	83%	0.71	457	0	11	50	12.72	7.82	4.72
5703084	47	M	22.3	Y	Y	3	2	Y	7	49	Y	10	0	Y	Y	N	69%	0.73	390	1	8	49	13.74	16.83	7.96

5661519	61	M	21.8	Y	Y	14	3	Y	14	168	N	N	1	Y	N	Y	48%	0.56	253	2	25	33	45.73	39.73	17.72	
5682204	42	M	26.1	Y	N	1	1	Y	8	42	Y	8	0	N	N	N	82%	0.73	419	1	9	50	16.86	18.62	7.26	
2984640	84	M	17.1	Y	Y	25	4	Y	22	330	N	N	3	N	Y	Y	22%	0.34	145	3	55	12	66.95	64.58	22.84	
5661888	45	F	24.2	N	Y	1	1	N			Y	10	0	Y	Y	N	80%	0.62	402	1	8	50	17.83	12.85	5.96	
5652811	59	F	24.3	N	Y	7	2	N			N	N	0	Y	Y	N	64%	0.55	320	2	15	47	18.84	15.66	6.95	
5659795	42	M	26.1	N	Y	1	1	Y	6	60	N	N	0	N	Y	N	81%	0.71	453	0	8	47	16.84	13.62	6.48	
5659658	53	M	22.54	Y	N	4	2	N			Y	12	0	N	N	N	67%	0.58	389	1	11	48	15.35	15.34	7.64	
5665356	63	M	21.2	Y	Y	9	2	Y	14	280	Y	14	1	Y	N	Y	63%	0.71	366	1	18	35	45.86	48.456	17.75	
5944747	52	M	24	Y	Y	3	1	Y	10	120	N	N	1	Y	N	Y	71%	0.75	420	0	9	47	15.34	13.64	6.87	
5902594	74	M	17.6	Y	Y	22	4	Y	22	330	Y	22	2	Y	Y	N	24%	0.34	142	3	11	15	64.65	55.4	18.63	
1203445	61	M	22.3	Y	N	5	2	Y	12	180	Y	15	1	Y	N	N	61%	0.71	394	1	13	46	17.56	11.75	7.4	
2462313	58	F	24.1	Y	Y	5	1	Y	8	80	N	N	0	Y	N	N	81%	0.69	421	0	10	43	15.65	12.81	7.19	
5919039	51	F	19.5	Y	Y	4	1	Y	12	120	N	N	1	Y	N	N	83%	0.71	410	1	12	43	16.54	4.87	8.35	
5920787	59	M	22.68	Y	Y	11	2	Y	13	195	N	N	1	Y	Y	N	65%	0.51	349	1	19	28	43.67	36.75	14.8	
5882333	45	M	21.4	Y	N	1	2	N			Y	14	0	N	Y	N	74%	0.65	444	0	11	47	15.38	12.48	6.03	
1064994	70	M	16.8	Y	Y	22	4	Y	20	320	Y	16	2	Y	Y	Y	25%	0.31	120	3	47	22	56.75	62.1	20.38	
5887242	54	M	18.2	Y	Y	4	2	Y	14	112	Y	8	1	Y	N	Y	68%	0.71	410	1	13	43	22.76	14.85	6.97	
5879988	53	M	21.85	Y	N	2	2	N			N	6	0	N	Y	N	71%	0.66	390	1	11	44	17.67	12.74	6.28	
5870764	70	F	27.23	Y	N	12	3	N			N	N	1	Y	N	N	37%	0.38	190	2	24	37	34.75	28.75	16.97	
5825237	74	M	16.1	Y	Y	18	4	Y	22	330	N	8	1	Y	Y	Y	26%	0.31	132	3	42	28	55.86	60.42	20.26	
5755254	45	F	22.3	N	Y	2	1	N			N	N	0	Y	N	N	83%	0.72	420	1	11	46	15.5	13.72	7.03	
1498847	59	M	22.3	Y	Y	8	2	Y	12	120	Y	12	1	Y	N	N	64%	0.57	380	1	16	40	22.97	16.85	7.03	
6018867	49	M	23.5	Y	N	1	1	N			N	N	1	N	Y	N	87%	0.68	430	0	9	38	16.54	16.5	7.93	
6015730	54	F	25.7	N	N	3	1	N			N	N	0	Y	N	N	84%	0.76	451	0	12	46	17.75	16.87	7.98	
6032754	71	M	18.2	Y	Y	18	3	N			N	13	0	Y	Y	Y	43%	0.51	230	2	34	48	56.86	54.86	17.49	
5755215	69	M	16.41	Y	N	20	3	Y	14	210	Y	12	1	Y	Y	Y	45%	0.46	189	2	45	22	54.45	49.65	17.4	
5646499	60	F	25	Y	Y	5	2	N			N	N	0	N	Y	N	75%	0.72	446	0	12	38	16.39	12.55	6.86	
6025039	79	M	16.2	Y	Y	22	4	Y	20	400	N	20	2	Y	N	N	23%	0.31	132	3	51	18	60.43	52.64	19.35	
5157929	67	M	22.23	y	y	12	2	y	14	112	y	15	1	Y	Y	N	68%	0.71	345	2	18	38	37.86	45.75	17.72	
5623134	60	M	29.54	Y	Y	13	3	Y	15	240	N	7	1	Y	Y	N	39%	0.35	248	2	19	38	35.87	43.94	18.45	
5264045	76	M	16.67	Y	Y	22	3	N			N	15	2	Y	N	N	46%	0.51	295	2	52	17	5.76	57.43	19.53	
5141790	85	M	19.5	Y	Y	17	3	Y	18	216	N	17	2	N	Y	Y	38%	0.41	230	2	40	22	48.86	49.35	17.53	
6023409	53	M	25	N	Y	2	1	Y	12	120	N	10	1	N	N	N	82%	0.75	436	0	10	47	17.45	12.85	5.42	
5986154	53	M	28.85	Y	Y	3	3	Y	8	64	N	8	1	N	Y	N	48%	0.434	377	2	13	48	16.6	15.86	7.35	
5989170	62	F	16.7	Y	Y	11	2	N			N	N	1	N	Y	N	68%	0.71	340	2	18	36	20.54	18.34	8.52	
5583417	60	F	21	N	Y	6	2	N			N	N	0	Y	Y	N	65%	0.58	362	1	15	38	17.35	16.87	7.54	