INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a disease state characterized by progressive airflow limitation and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking ***(GOLD, 2017).***

COPD is a common, preventable, treatable disease that characterize by persistent chest symptoms and airflow limitation due to air way or, and alveolar abnormalities.

The most common respiratory symptoms include dyspnea, cough, sputum. According to ***GOLD (2018)*** recommend that any patient has dyspnea, chronic cough, sputum production or history of exposure to risk factors of the disease should do spirometry to confirm the diagnosis of COPD exclude. Spirometry is required to make the diagnosis and the presence of post-bronchdilator FEV1/FVC<70 confirm the presence of persistent airflow limitation ***(GOLD, 2018).***

Chronic obstructive pulmonary disease COPD is common cause of morbidity and mortality worldwide. One third of patients detected using case finding approaches in primary care settings are asymptomatic or have mild symptoms ***(Lozano et al., 2010).***

However, in many patients, the disease is associated with several systemic manifestations that can effectively result in impaired functional capacity, worsening dyspnea, reduced

health related quality of life and increased mortality ***(Rabe et al., 2007).***

There are many studies that try to find asimple screening tools for early diagnosis and treatment of (COPD) such as (The PUMA Study) and (PLATINO Study), (The PUMA Study) is a simple questionnaire that include seven variables: sex, age, pack- years smoking, shortness of breath, expectoration, cough and previous use of spirometry, it was provided to at- risk subjects –defined ≥ 40 years, current or ex-smoker (≥10 pack – years or ≥ 50 pipes per year or ≥ 50 cigar per year). At- risk subjects with a PUMA score of ≥ 5 were considerd as high-risk and spirometry should be performed to confirm diagnosis, (PLATINO Study) is a study that depended on sex, age, educational level, BMI, smoking, exposure to dust and environmental pollution. The two studies are applied in latin America and shared in decrease the under diagnosis rate of (COPD) in latin America, the two studies use the spirometry to confirm the diagnosis of (COPD) ***(López et al., 2016).***

Underdiagnosis of COPD is serious problem in many countaries world-wide because there are no generally detection tools available to detect high-risk patients for spirometry. and patients will not go for COPD check-up until a serious issue happens like exacerbation.

Under diagnosis of (COPD) is a very serious problem today and under diagnosis of (COPD) is still high because of lack of information about (COPD) and delay of patients in seeking medical advices.

Aim of the Work

Trying to develop a new screening tool for early diagnosis of COPD.

Chapter 1
CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic Obstructive Pulmonary Disease, or COPD, refers to a group of diseases that cause airflow blockage and breathing-related problems ***(Decramer et al., 2012)***, it is a common preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases ***(GOLD, 2018).***

The chronic airflow limitation characteristic of COPD is caused by a mixture of small airways disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person. Chronic inflammation causes structural changes and narrowing of the small airways. Destruction of the lung parenchyma, also by inflammatory processes, leads to the loss of alveolar attachments to the small airways and decreases lung elastic recoil; in turn, these changes diminish the ability of the airways to remain open during expiration ***(Vestbo et al., 2013)***.

Epidemiology:

COPD is currently the fourth leading cause of death in the world but is projected to be the 3rd leading cause of death by 2020. More than 3 million people died of COPD in 2012 accounting for 6% of all deaths globally ***(Lozano et al., 2012).***

Tobacco smoking is the most important risk factor for the development of COPD; however, not all patients with COPD have a history of smoking. As little as 50% of cases worldwide are related to smoking, and an estimated 10%–12% of individuals with COPD have never smoked.

The prevalence of COPD varies greatly per country and also within different countries ***(Buist et al., 2008).*** This heterogeneity can be contributed to not only differences in diagnostic methods and classification but also to smoking habits, population age, environmental exposure such as biomass fuel exposure and air pollution, occupational exposure, prevalence of pulmonary tuberculosis, chronic asthma and socioeconomic status ***(Salvi and Barnes, 2009)***.

Statistical analysis of COPD prevalence in Egypt showed that 3 millions from the Egyptian population have COPD. In different studies prevalence were from 3.3% up to 10%. Prevalence rate in men was ~6.7% while it was ~1.5% in women ***(Adel et al., 2011).***

A study published in 2014 showed that the prevalence of COPD among high-risk Egyptians by GOLD criteria was 9.6% ***(Azza et al., 2014).***

COPD is strongly associated with activity limitations and an inability to work. Current smoking and lack of physical activity were both associated with greater percentages reporting

activity limitation and inability to work among those with COPD. COPD patients who smoke should be encouraged to quit and provided with the support they need to achieve this objective, whereas all COPD patients might benefit from pulmonary rehabilitation and a personalized exercise regimen.

Table (1): Factors influencing survival in patients with COPD

Risk Factor	Effect on survival
Post bronchodilator FEV_1	Decreases mortality with increased FEV_1, decreases mortality with reversible component of obstruction
Rate of FEV_1 decline	Decreases mortality with slower decline; FEV_1 <1 L generally considered severe disease
History of atopy	Decreases mortality
Higher diffusion capacity	Decreases mortality
PaO_2 level	Decreases mortality with increased level; PaO_2 <55 mm Hg increases mortality
Age	Increases mortality in older patients
Cigarette smoking	Increases mortality with continued use and greater consumption
Hypercapnia ($PaCO_2$ >45 mm Hg)	Increases mortality
Right-sided heart failure	Increases mortality
Resting tachycardia	Increases mortality

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume per second; PaO_2 = partial pressure of arterial oxygen; $PaCO_2$ = partial pressure of arterial carbon dioxide.

Adapted with permission from Hughes JR, Goldstein MG, Hurt RD, Shiffman S. Recent advances in the pharmacotherapy of smoking. JAMA 1999; 281: 72–6.

Pathology

Pathologically, COPD is characterized by involvement of large and medium, but especially, small airways, those with less than 2 mm in diameter ***(Hogg et al., 2004).*** In addition to inflammation, two other processes thought to be important in the pathogenesis of COPD: an imbalance of proteinases and antiproteinases in the lung, and oxidative stress ***(Rahman, 2005)***.

- *Central airways:*

(Trachea, bronchi > 2 mm internal diameter).

Inflammatory cells: Increase in number of macrophages, CD8 + (cytotoxic) T lymphocytes, few neutrophils or eosinophils.

Structural changes: Increase in number of goblet cells, enlarged submucosal glands (both leading to mucus hypersecretion), squamous metaplasia of epithelium ***(Saetta et al., 2001).***

- *Peripheral airways:*

(Bronchioles < 2mm internal diameter)

Inflammatory cells: Increase in number of Macrophages, T lymphocytes (CD8 > CD4), B lymphocytes, lymphoid follicles, fibroblasts, few neutrophils or eosinophils.

Structural changes: Airway wall thickening, peribronchial fibrosis, luminal inflammatory exudates, airway narrowing (obstructive bronchiolitis). Increased inflammatory response and exudate correlated with disease severity ***(Hogg et al., 2004).***

- *Lung parenchyma:*

Emphysema is classified pathologically into three major types:

a) Centriacinar emphysema:

In centriacinar emphysema respiratory bronchioles, alveolar ducts and the alveoli at the center of the acinus are destroyed but surrounding alveoli remain intact**.**

Centrilobular emphysema is associated with long standing cigarette smoking.

b) Panacinar emphysema:

Which involves the entire alveolus uniformly, this is the type of emphysema generally seen with homozygous $\acute{\alpha}_1$-antitrypsin deficiency. Focal panacinar emphysema at the lung bases may accompany centrilobular emphysema in smokers.

c) Distal acinar emphysema:

This involves distal airway structures, alveolar ducts and sacs with this form of emphysema, airflow is frequently well preserved ***(GOLD, 2015)***.

- *Pulmonary vasculature:*

Inflammatory cells:

Increase number of macrophages, T lymphocytes.

Structural changes:

Thickening of intima, endothelial cell dysfunction, Increase number of smooth muscle cells and pulmonary hypertension ***(Wright et al., 2005)***.

Pathophysiology

Pathologic changes in the lungs lead to corresponding physiologic changes characteristic of the disease, including:

Mucus hypersecretion and ciliary dysfunction lead to chronic cough and sputum production. These symptoms can be present for many years before other symptoms or physiologic abnormalities develop ***(Burgel and Nadel, 2004)***.

Expiratory airflow limitation best measured through spirometry, is the hallmark physiologic change of COPD and the key to diagnosis of the disease. It is primarily caused by fixed airway obstruction and the consequent increase in airway resistance. Destruction of alveolar attachments, which inhibits the ability of the small airways to maintain patency, plays a smaller role ***(O'Donnell et al., 2001)***.

In advanced COPD, peripheral airways obstruction, parenchymal destruction, and pulmonary vascular abnormalities reduce the lung's capacity for gas exchange, producing hypoxemia and, later on, hypercapnia ***(Wedzicha, 2002)*.**

Pulmonary hypertension, which develops late in the course of COPD (Stage III: Severe COPD), is the major cardiovascular complication of COPD and is associated with the development of corpulmonale and a poor prognosis ***(Barbera et al., 2003)***. The prevalence and natural history of corpulmonale in COPD are not yet clear ***(Wouters et al., 2002).***

Clinical presentation and diagnosis

A) History

Patients with COPD usually present with dyspnea, coughing or sputum production may or may not be present along with history of exposure to a predisposing factor (e.g. smoking). When expectorating sputum, it is important to assess whether sputum volume has increased and whether it is purulent (e.g. green). Purulent sputum is usually a sign of infection ***(Roche, 2010).***

B) Physical Examination:

A normal physical examination is frequent in early COPD. As the disease progresses some signs become apparent.

Investigations

A) For all patients:

Spirometry:

Diagnosis of COPD requires confirmation of an airflow limitation that is not fully reversible via spirometry and the history of a potentially causative exposure (e.g., smoking). Airflow limitation that is not fully reversible is defined by a low post bronchodilator FEV1/FVC ratio ***(Celli et al., 2004)***.

The threshold FEV1/FVC ratio that should be used to confirm an airflow limitation is uncertain. A post bronchodilator FEV1/FVC ratio of less than 0.7 has traditionally been the criterion for airflow limitation ***(Vestbo et al., 2013*)**.

Bronchodilator reversibility should be performed at least once to exclude asthma and to establish the best lung function for the individual patient, and to a lesser degree, to estimate the prognosis **(*Calverley et al., 2007*).**

Table (2): Spirometric classification of the severity of chronic obstructive pulmonary disease ***(GOLD, 2018)***

GOLD 1	**Mild**	FEV1 ≥ 0.80 predicted
GOLD 2	**Moderate**	0.50 ≤ FEV1 < 0.80 predicted
GOLD 3	**Severe**	0.30 ≤ FEV1 < 0.50 predicted
GOLD 4	**Very severe**	FEV1 < 0.30 predicted

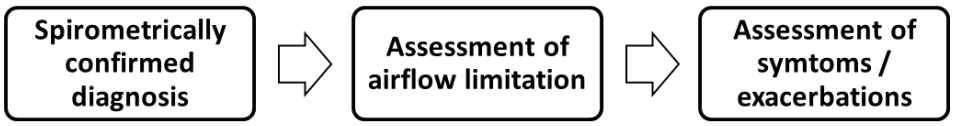
Assessment of symptoms:

In the past, COPD was viewed as a disease largely characterized by breathlessness. A simple measure of breathlessness such as the Modified British Medical Research Council (mMRC) Questionnaire (**Table 3**) was considered adequate, as the mMRC relates well to other measures of health status and predicts future mortality risk ***(Sundh et al., 2012)***

Table (3): Modified medical research council dyspnea scale.

Grade	Description
0	Not troubled with breathlessness, except during strenuous exercise.
1	Troubled by shortness of breath when hurrying or walking up a slight hill.
2	Walks slower than people of the same age due to breathlessness or has to stop for breath when walking at own pace on a level surface.
3	Stops for breath after walking about 100 m or after a few minutes on a level surface.
4	Too breathless to leave the house or breathless when dressing or undressing.

(Vestbo et al., 2013)



Exacerbation history		
≥ 2 or ≥1 leading to hospital admission	C	D
0 or 1 not leading to hospital admission	A	B
(GOLD, 2017)	mMRC 0-1 CAT < 10	mMRC ≥ 2 CAT ≥ 10

Figure (1): The refined ABCD assessment tool.

Chest radiography should be obtained in all patients. It is not sensitive for the diagnosis, but it is helpful in excluding other diseases and also of value to detect bullous disease ***(Fishman et al., 2003)***.

Hematocrit polycythemia can develop in the presence of arterial hypoxemia, especially in continuing smokers and can be identified by hematocrit > 52% in men and **>** 47% in women ***(Brian et al., 2011).***

Sputum examination In stable chronic bronchitis, sputum is mucoid and the predominant cell is macrophage. With exacerbation, sputum usually becomes purulent, with an influx of neutrophils. Gram stain usually shows a mixture of organisms; most common are hemophilus influenza and streptococcus pneumonia ***(Miravitlles et al., 2010).***

Electrocardiogram is abnormal in up to 75% of advanced COPD patients and it provides useful information about the presence of ischemic heart disease but is an insensitive method of assessing right ventricular hypertrophy **(*Gupta et al., 2011*)**.

B) Selected Patients:

α1-antitrypsin levels should be measured in young patients who develop COPD and have a strong family history. This may be followed by family screening. A serum value of α1-antitrypsin <15-20% of the normal limits is highly suggestive of homozygous α1-antitrypsin deficiency ***(GOLD, 2015).***

Management:

Smoking cessation:

Smoking cessation is the single most effective way to reduce the risk of developing COPD and stop its progression. Brief tobacco dependence treatment is effective and every tobacco user should be offered at least this treatment. Three types of counseling are especially effective: practical counseling, social support as part of treatment, and social support arranged outside of treatment. Several effective pharmacotherapies for tobacco dependence are available, and at least one of these medications should be added to counseling if necessary and in the absence of contraindications.

If effective resources and time are dedicated to smoking cessation, long-term quit success rates of up to 25% can be achieved ***(van Eerd et al., 2016).***

Vaccination:

Influenza vaccination can reduce serious illness (such as lower respiratory tract infections requiring hospitalization) ***(Wongsurakiat et al., 2004).***

Pneumococcal vaccinations, PCV13 and PPSV23, are recommended for all patients ≥ 65 years of age ***(Tomczyk et al., 2014).***

Pharmacological therapy:

Pharmacologic therapies can reduce symptoms, and the risk and severity of exacerbations, as well as improve health status and exercise tolerance.

Most of the drugs are inhaled so proper inhaler technique is of high relevance.

Bronchodilators:

Beta-2 agonists:

They relax airways by stimulating beta-2 adrenergic receptors, increasing cyclic AMP and produces functional antagonism to bronchoconstriction.

They are short-acting (SABA) and long-acting (LABA) beta agonists.

Formoterol and salmeterol are twice-daily beta2-agonists which improve FEV1 and lung volumes, dyspnea and exacerbation rate ***(Kew et al., 2013)*** but have no effect on mortality. Indacaterol is a once daily LABA that improves breathlessness ***(Han et al., 2013).*** Oladaterol and vilanterol are additional once daily LABAs.

Antimuscarinic drugs:

Antimuscarinic drugs block the bronchoconstrictor effects of acetylcholine on M3 muscarinic receptors expressed in airway smooth muscle.