THE PREVALANCE AND RISK FACTORS FOR IN-HOSPITAL MORTALITY AMONG COPD PATIENTS ADMITTED TO HOSPITAL UNIVERSITI SAINS MALAYSIA

BY

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ABBREVIATIONS

ABG	Arterial Blood Gas
ANCA	Anti Cytoplasmic Antibody
APACHE	Acute Physiology and Chronic Health Evaluation
BMI	Body mass index
COPD	Chronic Obstructive Pulmonary Disease
CT scan	Computed tomography scan
CXR	Chest x-ray
DLco	Diffusion capacity of carbon monoxide
ECHO	Echocardiography
ECG	Electrocardiogram
FBC	Full Blood Count
FEV1	Forced Expiratory Volume in 1 minute
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HUSM	Hospital Universiti Sains Malaysia
LVRS	Lung Volume Reduction Surgery
NETT	National Emphysema Treatment Trial
pO2	Partial pressure of oxygen
pCO2	Partial pressure of carbon dioxide
SpO2	Oxygen saturation
ICS	Inhaled corticosteroid
LABA	Long acting beta agonist

ENGLISH ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is still one of the leading causes of morbidity and mortality worldwide and it is the only disease which is showing increasing trend of mortality. However, the factors that determine the outcome of patients with COPD are still poorly understood, therefore it is very important to identify factors that influence patient's survival in order to plan for effective treatment strategy in reducing the morbidity and mortality.

The primary objective for this study is to estimate the prevalence of in-hospital mortality of COPD patients admitted to Hospital Universiti Sains Malaysia (HUSM). The secondary objective is to determine the risks of mortality among COPD patients who had been admitted to HUSM.

A total of 324 patients were recruited into this retrospective observational study. The prevalence of in-hospital mortality of COPD patients is 26.1%. The commonest cause of death was acute exacerbation of COPD which contribute 41% of total mortality, and the second commonest cause of death was cardiac related death (33%). The factors that had been identify to increase the risks of mortality in COPD after adjustment with multiple logistic analysis are smoking, duration of the disease, number of ICU admission, presence of pneumonia, level of serum albumin and the level of carbon dioxide arterial tension (pCO2).

In conclusion, the mortality rate of COPD patients is high and the mortality risks are smoking, duration of disease, number of ICU admission, presence of pneumonia, level of serum albumin and the of carbon dioxide arterial tension (pCO2).

ABSTRAK

Chronic Obstructive Pulmonary Disease (COPD) adalah salah satu penyebab kematian yang utama di seluruh dunia dan ia satu-satunya penyakit yang menunujukkan tahap peningkatan kematian setiap tahun. Walaubagaimanapun, faktor-faktor yang menyumbang kepada kematian pesakit COPD masih belum di ketahui dengan jelas, oleh itu adalah sangat penting untuk mengetahui faktor-faktor penyumbang ini supaya satu rancangan perawatan yang strategik dapat di wujudkan untuk mengurangkan kadar kematian.

Objektif utama kajian ini adalah untuk mengetahui prevalens kematian pesakit COPD yang di masukkan ke Hospital Universiti Sains Malaysia. Objektif yang kedua adalah untuk mengenalpasti faktor-faktor risiko kematian pesakit COPD.

Sejumlah 324 orang pesakit terlibat dalam kajian retrospektif ini. Prevalens kematian pesakit COPD yang di masukkan ke Hospital Universiti Sains Malaysia adalah tinggi iaitu 26.1%. Punca utama kematian adalah penyakit COPD itu sendiri iaitu 41% dan penyakit jantung adalah penyumbang kedua kematian iaitu 33%. Faktor-faktor yang telah di kenalpasti sebagai penyumbang kepada kematian pesakit COPD, setelah di analisis dengan analisis multivariate adalah perokok, tempoh penyakit COPD, jumlah kemasukan ke unit rawatan rapi, penyakit radang paru-paru (pneumonia), tahap albumin di dalam darah dan tahap gas karbon dioksida di dalam darah.

1. INTRODUCTION

1.1 Background

Chronic obstructive pulmonary disease (COPD) is one of leading causes of morbidity and mortality worldwide which results in an economic and social burden that is both substantial and increasing. According to World Bank Data, it is expected to move from its status in 2000 as the 4th and 12th most frequent cause of mortality and morbidity, respectively to be the 3rd and 5th leading cause of mortality and morbidity, respectively in 2020 (Gunen et al 2005). It is the only major disease showing increasing trends of mortality.

The prevalence of COPD is usually underestimated because the disease is not diagnosed until it is clinically apparent and moderately advanced. Factors that determine the outcomes of patient with COPD are poorly understood. Identification of the factors that may influence survival in patients with COPD may enable clinicians to better asses life expectancy. This is extremely important, in that it may help offset the social and economic burden of COPD through the implementation of more individualized and effective treatment strategies as well as better mobilizing health care resources (Gunen et al 2005)

1.2 Epidemiology

Chronic obstructive pulmonary disease (COPD) affects over 5% of the adult population (Qaseem A et al 2007). With the NHANES III (Third National Health and Nutrition Examination Survey), the prevalence of COPD can be determined. The GOLD ((Global Initiative for Chronic Obstructive Lung Disease) definition of COPD (stage 1 and higher) resulted in prevalence estimates of 23.6 million adults aged 18 and older (13.9%) with COPD. An estimated 2.4 millions of these adults or 1.4% of the population had GOLD stage 3 or 4 with an FEV1 of less than 50% of the predicted value (Mannino et al 2007).

Prevalence, incidence, and mortality rates increase with age. Prevalence is higher in men, but total mortality is similar in both sexes. Incidence and mortality are generally higher in whites, blue-collar workers, and people with fewer years of formal education, probably because these groups have a higher prevalence of smoking. COPD also seems to occur in families of α_1-antitrypsin (α_1-antiprotease inhibitor) deficiency.

COPD is increasing worldwide because of the increase in smoking in developing countries, the reduction in mortality due to infectious diseases, and the widespread use of biomass fuels.

1.3 Definition

1.3.1 Chronic Obstructive Pulmonary Disease (COPD)

The GOLD (Global Initiative for Chronic Obstructive Lung Disease) has defined chronic obstructive pulmonary disease (COPD) as a preventable and treatable disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences.

Chronic obstructive pulmonary disease (COPD) comprises chronic obstructive bronchitis (clinically defined) and emphysema (pathologically defined). Many patients have features of both.

1.3.2 Chronic bronchitis

Chronic obstructive bronchitis is chronic bronchitis with airflow obstruction. It is also called chronic mucous hypersecretion syndrome and is defined as productive cough for at least 3 month total duration in 2 successive years. Chronic bronchitis becomes chronic obstructive bronchitis if spirometric evidence of airflow obstruction develops.

1.3.3 Emphysema

Emphysema is destruction of lung parenchyma leading to loss of elastic recoil and loss of alveolar septa and radial airway traction, which increases the tendency for airway collapse. Lung hyperinflation, airflow limitation, and air trapping follow. Airspaces enlarge and may eventually develop bullae.

1.3.4 COPD exacerbation

Exacerbation is defined as an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day to day variation, is acute in onset and may warrant a change in regular medication in a patient with underlying COPD (GOLD guideline 2007)

1.4 Etiology

1.4.1 Cigarette smoking

Tobacco smoke is by far the most important risk factor for COPD worldwide, although only about 15% of smokers develop clinically apparent COPD. An exposure history of 40 or more pack-years is especially predictive. Cigarette smokers have a higher prevalence of respiratory symptoms and lung function abnormalities, a greater annual rate of decline in FEV1 and a greater COPD mortality rate than nonsmokers.

In the Lung Health Study, middle-aged smokers who continued smoking had an accelerated loss in FEV_1 compared with nonsmokers. In addition, individuals with COPD are at increased risk of death from other causes, such as lung cancer and cardiovascular disease.

1.4.2 Exposure to biomass smoke

Smoke from burning biomass fuels for indoor cooking and heating is an important contributing factor in developing countries. Smokers with preexisting airway reactivity, even in the absence of clinical asthma, are at greater risk of developing COPD.

1.4.3 Genetic predisposition

Genetic factors also play an important role in COPD. The best-defined genetic disorder is α_1-antitrypsin deficiency which is an important cause of emphysema in nonsmokers and influences susceptibility to disease in smokers. Polymorphisms in microsomal epoxide hydrolase, vitamin D–binding protein, IL-1β, IL-1 receptor antagonist, phospholipase A2,

matrix metalloproteinase 9, and *ADAM-33* genes are all associated with rapid decline in forced expiratory volume in 1 sec (FEV_1) in selected populations.

1.4.4 Infection

Infection, in conjunction with cigarette smoking, may amplify progression of lung destruction. The inflammation in COPD increases with increasing disease severity, and, in severe disease, inflammation may not resolve completely with smoking cessation. This inflammation also not appears to be responsive to corticosteroids.

Bacteria, especially Haemophilus influenzae, colonize the normally sterile lower airways of about 30% of patients with COPD. In more severely affected patients (eg, those with previous hospitalizations), Pseudomonas aeruginosa colonization is common. Smoking and airflow obstruction may lead to impaired mucus clearance in lower airways, which predisposes to infection. Repeated bouts of infection increase the inflammatory burden that hastens disease progression. There is no evidence that long-term use of antibiotics slows the progression of COPD in susceptible smokers.

1.4.5 Others

Low body weight, childhood respiratory diseases, passive cigarette smoke exposure, air pollution, and occupational dust (eg, mineral dust, cotton dust) or chemical (eg, cadmium) exposure also contribute to the risk of COPD but are of minor importance compared with cigarette smoking.

1.5 Pathophysiology

The cardinal pathophysiologic feature of COPD is airflow limitation caused by loss of elastic recoil as a result of emphysema, or airflow obstruction caused by mucus hypersecretion, mucus plugging, mucosal edema, bronchospasm, or all of these mechanisms.

Inhalational exposures trigger an inflammatory response in airways and alveoli that leads to disease in genetically susceptible people. The process is thought to be mediated by an increase in protease activity and a decrease in antiprotease activity. Lung proteases, such as neutrophil elastase, matrix metalloproteinases, and cathepsins, break down elastin and connective tissue in the normal process of tissue repair. Their activity is balanced by antiproteases, such as α_1-antitrypsin, airway epithelium–derived secretory leukoproteinase inhibitor, elafin, and matrix metalloproteinase tissue inhibitor.

In people with COPD, activated neutrophils and other inflammatory cells release proteases as part of the inflammatory process; protease activity exceeds antiprotease activity, and tissue destruction and mucus hypersecretion result. Neutrophil and macrophage activation also leads to accumulation of free radicals, superoxide anions, and hydrogen peroxide, which inhibit antiproteases and cause bronchoconstriction, mucosal edema, and mucous hypersecretion. Neutrophil-induced oxidative damage, release of profibrotic neuropeptides (eg, bombesin), and reduced levels of vascular endothelial growth factor may contribute to apoptotic destruction of lung parenchyma.

This will result in parenchymal tissue destruction (resulting in emphysema) and disrupt normal repair and defense mechanisms (resulting in small airway fibrosis). These

pathological changes lead to air trapping and progressive airway limitation. COPD comprises pathological changes in four different compartments of the lungs (central airways, peripheral airways, lung parenchyma and pulmonary vasculature), which are variably present in individuals with the disease Increased airway resistance increases the work of respiration and lung hyperinflation. Increased work of breathing may lead to alveolar hypoventilation with hypoxia and hypercapnia, although hypoxia is also caused by ventilation/perfusion (V/Q) mismatch; increased caloric expenditure and weight loss may occur. Some patients with advanced disease develop chronic hypoxemia and hypercapnia. Chronic hypoxemia increases pulmonary vascular tone which, if diffuse, causes pulmonary hypertension and cor pulmonale. COPD has a variable natural history and not all individuals follow the same course.

1.6 Symptoms

The diagnosis of COPD should be considered in any patient who has the following symptoms: cough with sputum production; or dyspnoea; or history of exposure to risk factors for the disease. COPD takes years to develop and progress. Most patients have smoked ≥ 20cigarettes/day for > 20 years. Productive cough usually is the initial symptom, developing among smokers in their 40s and 50s. Dyspnea that is progressive, persistent, exertional, or worse during respiratory infection appears years later, by the time patients reach their late 50s or 60s.

Symptoms usually progress quickly in patients who have higher lifetime tobacco exposure. Morning headache develops in more advanced disease and signals nocturnal hypercapnia or hypoxemia. Systemic features of COPD, particularly in patients with severe disease include cachexia, skeletal muscle wasting, increased risk of cardiovascular disease, anemia, osteoporosis and depression.

1.7 Signs

A physical examination is rarely diagnostic in COPD. Physical signs of airflow limitation are usually not present until significant impairment of lung function has occurred, and their detection has low sensitivity and specificity. Signs of COPD include wheezing, increased expiratory phase of breathing, lung hyperinflation manifested as decreased heart and lung sounds, and increased anteroposterior diameter of the thorax (barrel chest).

Signs of advanced disease include pursed-lip breathing, accessory muscle use paradoxical indrawing of the lower intercostal interspaces during inspiration and cyanosis. Signs of cor pulmonale include neck vein distention; splitting of the 2nd heart sound with an accentuated pulmonic component, tricuspid insufficiency murmur and peripheral edema. Right ventricular heaves are uncommon in COPD because the lungs are hyperinflated. Spontaneous pneumothorax may occur as a result of rupture of bullae and should be suspected in any patient with COPD whose pulmonary status abruptly worsens.

1.8 Diagnosis

Diagnosis is suggested by history, physical examination and chest imaging and is confirmed by pulmonary function tests. Differential diagnosis includes asthma, heart failure and bronchiectasis.

1.8.1 Pulmonary Function Test

Patients suspected of having COPD should undergo complete pulmonary function testing to confirm airway obstruction, to quantify its severity and reversibility, and to distinguish COPD from other diseases. It is also useful for following disease progression and monitoring response to treatment. The primary diagnostic tests are FEV1, which is the volume of air forcefully expired during the first second after a full breath; forced vital capacity (FVC), which is the total volume of air expired with maximal force; and flow-volume loops, which are simultaneous spirometric recording of airflow and volume during forced maximal expiration and inspiration.

Reductions of FEV1, FVC and the ratio of FEV1/FVC are the hallmark of airway obstruction. FEV1/FVC < 0.7 confirms the presence of airflow limitation. FEV1 declines up to 60 mL/yr in smokers compared with a less steep decline of 25 to 30 mL/yr in nonsmokers, beginning at about age 30. In middle-aged smokers who already have a low FEV1, the decline occurs more rapidly. When the FEV1 falls below about 1 L, patients develop dyspnea with activities of daily living (although dyspnea is more closely related to the degree of air trapping than to the degree of airflow limitation). When the FEV1 falls below about 0.8 L, they are at risk of hypoxemia, hypercapnia and cor pulmonale. Normal reference values are determined by patient age, sex, height and race.