SURVIVAL, HEALTHCARE UTILIZATION, AND COSTS ASSOCIATED WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE AMONG SEER-MEDICARE BENEFICIARIES WITH NON-SMALL CELL LUNG CANCER

by

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ABSTRACT

SHWETA SHAH. Survival, healthcare utilization and costs associated with chronic obstructive pulmonary disease among SEER-Medicare beneficiaries with non-small cell lung cancer. (Under the direction of DR. CHRISTOPHER M. BLANCHETTE)

Lung cancer and chronic obstructive pulmonary disease (COPD) are among leading causes of morbidity and mortality worldwide. We investigated the impact of pre-existing COPD and its subtypes, chronic bronchitis and emphysema, on overall survival among Medicare enrollees diagnosed with non-small cell lung cancer (NSCLC). We also assessed healthcare utilization and costs in elderly NSCLC patients with and without pre-existing COPD. Using SEER-Medicare data, we included patients >= 66 years of age diagnosed with NSCLC at any disease stage between 2006 to 2010 and continuously enrolled in Medicare Parts A and B in the 12 months prior to diagnosis. Pre-existing COPD in patients with NSCLC were identified using ICD-9 codes. Kaplan-Meier method and log-rank tests were used to examine overall survival by COPD status and COPD subtype. Multivariable Cox Proportional Hazards models were fit to assess the risk of death after cancer diagnosis. The adjusted analysis was performed using a generalized linear model for healthcare costs and a negative binomial model for healthcare utilization. NSCLC patients with pre-existing COPD had shorter survival with marked differences in early stages of cancer. Chronic bronchitis demonstrated a greater association with time to death than emphysema. Healthcare utilization and costs among lung cancer patients with pre-existing COPD was approximately two to three times higher than the Non-COPD group.

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CHAPTER 1: BACKGROUND

Lung cancer and chronic obstructive pulmonary disease (COPD) are among leading causes of morbidity and mortality worldwide. Lung cancer is the second most common cancer in both men and women. The American Cancer Society estimates 224,390 new cases of lung cancer in the United States (US) in 2016. More people die of lung cancer than breast, prostrate, and colon cancer combined. It accounts for 27% of all cancer deaths making it the leading cause of cancer mortality. The lifetime risk of developing lung cancer in men is 1 in 14 and for women, it is 1 in 17. Lung cancer mainly occurs in older people. About 2 out of 3 people diagnosed with lung cancer are 65 or older, while less than 2% are younger than 45. Five-year survival rates are low compared to other common cancers at 16.3 percent. About 80% of lung cancers are non-small cell lung cancers (NSCLC). (1)

Non-Small Cell Lung Cancer (NSCLC)

Lung cancers are classified based on cellular histology. (2) The histologic classification is important and useful for guiding management of the disease as well as predicting disease outcomes. Broadly, lung cancers are classified into two types as: small cell lung cancers (SCLC) and non-small cell lung cancers (NSCLC). SCLC account for about 10%-15% of lung cancers. NSCLC is the most common lung cancer, comprising about 85% of all cases. The three main types of NSCLC are determined by the type of

cells found in the tumor. Adenocarcinomas are the most common type of NSCLC in the United States and they account for 40% of lung cancer cases. Squamous cell carcinomas comprise 25% to 30% of all lung cancer cases. Large cell carcinomas, also called as undifferentiated carcinomas, are the least common type of NSCLC, comprising 10%-15% of all lung cancers. (3)

According to the American Cancer Society, the 5-year survival rate for NSCLC specifically is 21%. For patients with stage IA and IB NSCLC, the 5-year survival rate is about 49% and 45% respectively. It is 30% for patients in stage IIA cancer and 31% for stage IIB cancer. The 5-year survival rate is about 14% for stage IIIA, and about 5% for stage IIIB. NSCLC is typically difficult to treat when the cancer spreads outside of the lungs. For stage IV NSCLC, the 5-year survival rate is about 1%. (4)

Chronic Obstructive Pulmonary Disease

COPD is a group of respiratory conditions, including phenotypes chronic bronchitis and emphysema, which are progressive and debilitating. COPD is characterized by difficulty in breathing, lung airflow limitations, cough, and other symptoms. (5) According to the American Lung Association, COPD is the third leading cause of death in the US after cancer and heart disease. In 2010, COPD accounted for 134,676 deaths in the US. (6) According to the 2011 National Health Interview Survey, an estimated 12.7 million adults (5.5%) had been diagnosed with COPD. There was an increase in the prevalence of COPD from 3.2% among those aged 18–44 years to >11.6% among those aged ≥65 years. (7) Previous studies have indicated that COPD is underdiagnosed and that up to 24 million Americans have evidence of impaired lung

function. (7) COPD is a major public health problem due to its high incidence and related morbidity and mortality and pose significant health and economic burdens on society.

The two main phenotypes of COPD are chronic bronchitis and emphysema. Chronic bronchitis is caused by bronchial inflammation and recurrent infection in the lungs. Clinically, chronic bronchitis presents as persistent cough that produces sputum and mucus, for at least three months per year in two consecutive years. (6) In 2011, more than 10 million Americans were diagnosed with chronic bronchitis. Seventy percent of these patients were over age 45. The risk of chronic bronchitis increased with age. In 2011, the prevalence rate was lowest among patients aged 18 to 44 years at 28.6 per 1,000 persons and highest among patients over 65 years at 64.2 per 1000 persons. (7) Emphysema is a progressive long term obstructive disease of the lung characterized by degradation of the alveoli which are important for oxygen exchange between the air and the bloodstream. The disease is characterized by increased shortness of breath and loss of elasticity in the intact alveolar walls (6). According to the American Lung Association, 4.7 million Americans had emphysema in 2011 with a lifetime prevalence rate of 20.2 per 1000 persons. More than 90% of patients were over age 45. (7)

Cachexia

Cancer Cachexia is also known as cancer anorexia-cachexia. It is a combination of both starvation caused by anorexia and wasting syndrome due to cachexia. (8) It is a debilitating condition characterized by involuntary loss of weight, muscle wasting, and loss of appetite. (9) Patients suffering from cancer cachexia have a poor quality of life, and experience pain and fatigue. Moreover, among cancer patients, cachexia contributes

to poor response to chemotherapy and poor surgical and clinical outcomes. (9) In advanced stages of cancer, cachexia cannot be cured by increasing food intake or nutritional supplements. (10)

Cachexia affects most patients with advanced cancer and the prevalence of cancer anorexia-cachexia depends on the type of cancer. (11) Vaughan et al highlighted that 50% to 85% of patients with gastrointestinal, pancreatic, lung, and colorectal cancer have weight loss at the time of cancer diagnosis and before treatment. (12) In the United States, it is estimated that more than 1.3 million people have cancer anorexia-cachexia. Moreover, cancer cachexia is responsible for 20% of all cancer deaths, contributing to more than 7.4 million deaths worldwide each year.(13) In industrialized countries (North America, Europe, Japan), the overall prevalence of cachexia (due to any disease) is growing and currently about 1%, i.e., about nine million patients.(11)

As cachexia is a syndrome, defining cachexia has been a challenge due to multiple definitions in the literature. In 2011, an international consensus statement on cancer cachexia highlighted three diagnostic criteria: (1) unintentional weight loss (>5% over past 6 months in absence of simple starvation); (2) weight loss >2% when BMI was <20 kg/m^2; and (3) appendicular skeletal muscle index consistent with sarcopenia and any weight loss > 2%. (8)

Cachexia is a severe complication of cancer associated with an increase of adverse events of chemotherapy, fewer cycles of chemotherapy, a lower response to therapy, and decreased survival.(14) Suzuki et al estimated that more than 20% of cancer patients died due to cachexia, and more than 50% of patients died with cachexia.(14) In another study by Bennanl-Balti N et al, patients indicated that their quality of life was

affected more by weight loss and poor nutritional status than by the cancer itself. (10) Cachexia affects majority of cancer patients and therefore poses significant burden on the patients as well as the healthcare system. About 15--40% of patients with COPD experience muscle wasting depending on the stage of the disease. (15) Prior studies have shown that muscle wasting not only contributes to diminished skeletal muscle function, reduced exercise capacity, and decreased health status, (16, 17) but is also a determinant of mortality in COPD, independent of airflow obstruction. (18, 19)

Link between COPD and Lung Cancer

The Lung Health Study Research showed that air flow obstruction among lung cancer patients was the most common cause of death. The prevalence of COPD in newly diagnosed lung cancer patients was six times higher than in smokers without lung cancer. Lung cancers are more common among smokers with a prior diagnosis of COPD compared to smokers with normal lung function. (20) In a case-control study, Young et al suggested that impaired lung function may be more important than age or even smoking history as a predictor of lung cancer. (21) A meta-analysis conducted in 2005 concluded that even a small reduction in airflow significantly predicted lung cancer. (22) Findings from another study showed that a 10% reduction in lung function was associated with an almost 3 times increase in lung cancer risk. (23)

COPD and lung cancer may have common origins in inflammation. They may also share the same genetic predispositions and environmental risk factors, with exposure to tobacco smoke being the primary risk factor. (24) Not all patients with the same exposure to tobacco smoke develop lung cancer and COPD.

Genetic predisposition: Even though environmental exposure and tobacco cigarette smoke play a key role in lung cancer and COPD pathogenesis, only a small proportion of smokers will develop both or either disease. This suggests that genetic predisposition may contribute to susceptibility to disease. (25) Genetic studies have identified the deficiency of alpha1 antitrypsin (AATD) caused by mutations in SERPINA1 gene. (26) AATD is a hereditary disorder characterized by low serum levels of alpha-1-antitrypsin (AAT). (27) This leads to protein degradation and increased inflammation, leading to an increased risk of COPD. (28)

Cell Cycle Regulation: A common feature among lung cancer patients with COPD is an increased resistance to pro-apoptotic stimuli. (29) Apoptosis is a physiological process that eliminates unwanted cells and provides space for new cells during the process of cell renewal. (30) Some lung cells may fail to arrest or apoptose due to mutations or epigenetic changes in the cell cycle mechanism. This might increase the population of lung epithelial cells from which tumors could arise. (25)

Inflammation: Tobacco smoke can cause inflammation leading to COPD. All smokers develop macrophage and neutrophil infiltration in their lungs. Chronic inflammation could result in repeated injury and uncontrolled cell growth leading to the development of lung cancer. (31) Moreover, chronic inflammation among patients with COPD may activate the proteins that promote cancer growth and deactivate the proteins required for DNA repair. (32) Prior research has shown that destructive inflammatory cell infiltrates that are operative in emphysema are found in both airways and airspaces that could promote the development of proximal and distal lung cancer. (33)

Economics of Lung Cancer and COPD

Lung cancer and COPD take a heavy toll on the US economy. According to the National Institutes of Health, the total direct medical cost of cancer in the United States was $124.6 billion in 2010. It is estimated that approximately $12.6 billion are spent in the country on lung cancer treatment alone. Lost productivity due to early death from cancer lead to an additional $134.8 billion in 2005, of which $36.1 billion was caused by lung cancer. (34) Previous estimates of COPD related medical costs in the US have indicated high costs incurred by patients with $37.2 billion in 2004 and $42.6 billion in 2007. (35) According to the National Heart Lung and Blood Institute, the national projected annual cost for COPD in 2010 was $49.9 billion This includes $29.5 billion in direct health care expenditures, $8.0 billion in indirect morbidity costs and $12.4 billion in indirect mortality costs. (36) A study conducted by Ford et al in 2010 estimated total national medical costs attributable to COPD at $32.1 billion dollars annually. Absenteeism costs were $3.9 billion accounting for a total burden of $36 billion in COPD-attributable costs. Moreover, 18% of the medical costs were paid for by private insurance, 51% by Medicare, and 25% by Medicaid. The study also projected a rise in medical costs from $32.1 billion in 2010 to $49 billion by 2020. (37)

Rationale for the Study

Lung cancer remains one of the most fatal forms of cancer. Screening of COPD patients for the development of cancer, for example through CT scans, has been suggested as a potential method to enable early detection and thereby to improve outcomes. (38) One of the most important factors influencing the survival of patients with

lung and bronchus cancers is the selection of an appropriate course of therapy based on the assessment of patient risk. However, the selection of a course of therapy currently is largely based on cancer stage alone despite the contribution of other factors to patient survival. It is important to investigate if COPD is a potential prognostic factor of lung cancer as well as individually assess the impact of COPD phenotypes: chronic bronchitis and emphysema. This knowledge will be useful in early detection of lung cancers as well as incorporating treatment selection in early and advanced cancer.

Approximately 10% of patients diagnosed with NSCLC die from cancer cachexia. (11) Cachexia is associated with a continuum starting at pre-cachexia stage through refractory cachexia with the possibility of reversibility in the pre-cachexia stage. (39) A more thorough understanding of the pathophysiology of cachexia development and progression is needed that will likely guide treatment approaches. Moreover, no studies have examined the onset of cachexia among COPD patients by phenotype among elderly patients with NSCLC. Information on determining the onset of cachexia during lung cancer would help in early detection and intervention of this wasting syndrome.

As the median age of diagnosis of lung cancer patients is high (71 years), the cost is largely incurred by the US Medicare system. Despite this burden and its expected future trend, limited data exist comparing health care resource use and costs in elderly patients with NSCLC and COPD. Most existing cost studies focus on NSCLC alone (40,41,42) or on all lung cancers combined. (43,44,45) Existing cost studies have primarily focused on estimations of chemotherapy use and costs (46, 47, 48) with little information presented regarding broader treatment patterns, resource utilization, and

costs for other service categories. Moreover, most cost-related studies fail to account for censoring and present overall mean values which may not be true reflection of costs.

To address these information needs, the current study will employ retrospective analysis of linked Surveillance, Epidemiology and End Results (SEER)-Medicare database to examine survival, risk of cachexia, healthcare utilization and costs in elderly NSCLC patients with and without pre-existing COPD.

CHAPTER 2: SURVIVAL ASSOCIATED WITH COPD AMONG NSCLC

Introduction

Lung cancer and chronic obstructive pulmonary disease (COPD) are among leading causes of morbidity and mortality worldwide. Lung cancer is the second most common cancer in both men and women. The American Cancer Society estimates 224,390 new cases of lung cancer in the United States (US) in 2016. More people die of lung cancer than breast, prostrate, and colon cancer combined. It accounts for 27% of all cancer deaths making it the leading cause of cancer mortality. About 2 out of 3 people diagnosed with lung cancer are 65 or older, while less than 2% are younger than 45. Five-year survival rates are low compared to other common cancers at 16.3 percent. About 80% of lung cancers are non-small cell lung cancers (NSCLC). (1)

According to the American Lung Association, COPD is the third leading cause of death in the US after cancer and heart disease. In 2010, COPD accounted for 134,676 deaths in the US. (2) According to the 2011 National Health Interview Survey, an estimated 12.7 million adults (5.5%) had been diagnosed with COPD. (3) Previous studies have indicated that COPD is underdiagnosed and that up to 24 million Americans have evidence of impaired lung function. (4) The two main subtypes of COPD are chronic bronchitis and emphysema. Chronic bronchitis is caused by bronchial inflammation and recurrent infection in the lungs. The risk of chronic bronchitis increased with age. (2)

In 2011, the prevalence rate was lowest among patients aged 18 to 44 years at 28.6 per 1,000 persons and highest among patients over 65 years at 64.2 per 1000 persons. (3) Emphysema is a progressive long term obstructive disease of the lung characterized by degradation of the alveoli that promote oxygen exchange between the air and the bloodstream. (2) According to the American Lung Association, 4.7 million Americans had emphysema in 2011 with a lifetime prevalence rate of 20.2 per 1000 persons. More than 90% of patients were over age 45. (3)

COPD has been suggested as a risk factor for the development of lung cancer. The Lung Health Study Research showed that air flow obstruction among lung cancer patients was the most common cause of death. (5) In a case-control study, young et al suggested that impaired lung function may be more important than age or even smoking history as a predictor of lung cancer. (6) A meta-analysis conducted in 2005 concluded that even a small reduction in airflow significantly predicted lung cancer. (7) Findings from another study showed that a 10% reduction in lung function was associated with an almost 3 times increase in lung cancer risk. (8)

Although COPD is consistently associated with lung cancer, the association between pre-existing COPD among NSCLC across different stages of lung cancer remains unclear. We investigated the impact of pre-existing COPD as well as its subtypes: chronic bronchitis and emphysema on survival in different stages of NSCLC among elderly patients. This knowledge will be useful in early detection of lung cancers as well as incorporating treatment selection in early and advanced cancer.

Methods

Data sources

The source of data for this study was the Surveillance, Epidemiology, and End Results (SEER)- Medicare linked database. This database combines information from two sources, the National Cancer Institute's (NCI) SEER program and the Center for Medicare-Medicaid Services claims data through a linking process to allow researchers to view clinical and administrative data for a single patient across time and settings of care. The SEER Program collects information on all patients diagnosed with cancer within 18 geographically defined areas in the USA. Altogether, the SEER Program covers approximately 28% of the US population. Information collected includes patient demographics, tumor characteristics, stage, and survival status (9) and the quality of data is considered highly valid according to the North American Association of Central Cancer Registries. (10)

Medicare is the federal health insurance program for 97% of the US population 65 years and older. Medicare enrollees become eligible for services covered by Medicare from patient's program eligibility to their death. The claims data contain multiple data files of which three were used for data acquisition in the current study. The Medicare Provider Analysis and Review (MEDPAR) file covers Part A inpatient hospitalizations and skilled nursing facility claims. The Carrier Claims (or National Claims History (NCH)) file includes all Part B provider claims (e.g. physicians, nurse practitioners, ambulance providers, clinical laboratories, etc.). The Outpatient file includes claims from outpatient providers (e.g. hospital outpatient departments, rural health clinics, outpatient rehabilitation, etc.). (11) The linkage of the SEER data with the Medicare data entails

matching incident cancer cases reported in the SEER data with a master file of Medicare enrollment. (12)

Study population

Patients were eligible for inclusion in the study if diagnosed with first primary lung cancer between January 1, 2005 and December 31, 2010, at least 66 years of age, and continuously enrolled in Medicare Parts A and B in the 12 months prior to diagnosis. Patients were excluded if their date of death was recorded prior to or the same month as diagnosis, if they were diagnosed by autopsy, death certificate, or in an unknown month, and if they were enrolled in a health maintenance organization (HMO) at any time during the 12 months prior to diagnosis (because complete claims data were unavailable for these patients).

Study variables

SEER program registries routinely collect data on patient demographics (age, race/ethnicity, residence, and socioeconomic status, primary tumor site, tumor morphology, and stage at diagnosis) among other variables. Lung cancer diagnosis was based on the International Classification of Disease for Oncology (3rd edition, ICD-O-3) histology codes in the SEER data. Tumor stage was classified according to the sixth edition of the American Joint Commission on Cancer manual for patients diagnosed between 2005 and 2010.

The diagnosis of pre-existing chronic obstructive pulmonary disease (COPD) in lung cancer patients were identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes (491 [chronic bronchitis], 492 [emphysema], 496 [chronic airway obstruction, not elsewhere classified]) before cancer

diagnosis date through the Medicare claim files. These codes were chosen based on support from previous literature as successful identifiers of COPD. (13)

The Deyo modification of Charlson's index was used to identify the 15 non-cancer comorbidities from the Charlson Comorbidity Index. (14) The index accounts for the number and seriousness of the conditions and a higher score indicates a greater burden of comorbid disease. These comorbidities were defined using criteria provided by the NCI for use with diagnoses reported within MEDPAR files, outpatient file, and physician claims data. (15, 16)

Statistical analysis

Demographic and clinical characteristics of lung cancer patients were summarized descriptively by pre-existing COPD status (COPD vs. Non COPD). Further analysis of COPD subtype was also performed which included lung cancer patients with pre-existing chronic bronchitis and emphysema. For the subtype analysis, patients identified with the ICD-9-code 496 (chronic airway obstruction, not elsewhere specified) were excluded from the analysis. Descriptive statistics (i.e. counts, frequencies, averages) were used to identify population and cohort characteristics. Chi-square test for categorical variables and ANOVA or t-tests for continuous variables determined differences between groups.

Overall survival was measured from date of lung cancer diagnosis to date of death. The date of death was assigned by using the Medicare date or SEER date of death if Medicare date was missing. All other patients were assumed to be alive at the end of the follow-up period (December 31, 2010), although they may have been censored earlier for other reasons. In the overall survival analysis, comparisons were made between lung cancer patients with pre-existing COPD and Non-COPD for every stage of cancer (Stage

I to Stage IV). Similarly, in the subtype analysis, overall survival was compared in lung cancer patients with pre-existing chronic bronchitis, emphysema, and Non-COPD for every stage of cancer. Stage IIIA and Stage IIIB for lung cancer were categorized as Stage III.

Kaplan Meier method and corresponding log rank tests were used to examine overall survival by COPD status as well as COPD subtype. To assess the risk of death after cancer diagnosis, multivariate survival analysis was completed by cox proportional hazards regression model. Statistical significance was established at $P <= 0.05$. SAS 9.4 (SAS Institute Inc, Cary, North Carolina) was used for all data analyses. The conduct of this study was approved by NCI and the Institutional Review Board at the University of North Carolina at Charlotte.

Results

We identified 66,963 lung cancer patients. Of these, 22,497 (33.60%) had COPD before lung cancer diagnosis. Patients differed statistically ($P<0.001$) across all demographic characteristics between pre-existing COPD and Non-COPD lung cancer patients (Table 1). The mean age of pre-existing COPD patients (75 years) was similar to Non-COPD patients. The majority of patients in the COPD (51.68%) and Non-COPD (51.08%) group were males. Caucasians accounted for the greatest proportion of lung cancer patients in both groups (90.74% and 86.46% respectively) followed by African-Americans (6.71% and 8.30%). The most common comorbid conditions among COPD and Non-COPD groups were congestive heart failure (11.50% and 8.61%), diabetes mellitus (10.47% and 11.71%), peripheral vascular disease (6.19% and 4.53%) and

cerebrovascular disease (4.45% and 5.09%). The comorbidity status of both groups, measured by the Charlson's Comorbidity Index (CCI), was statistically significant. Approximately 96% of patients accounted for CCI score less than 3 in COPD and Non-COPD groups.

Nearly all COPD and Non-COPD patients (approximately 99%) had invasive tumors. Approximately 22% of COPD patients had poorly differentiated tumor grade compared with 21% of patients in the Non-COPD group. Among COPD patients, 36.34% had stage IV lung cancer compared with 44.25% in the Non-COPD group.

For COPD subtype analysis, among 22,497 lung cancer patients with pre-existing COPD, 11,221 (18.97%) had chronic bronchitis and 3475 (5.87%) patients had emphysema. We excluded 7801 patients that were identified with the ICD-9-code 496 (chronic airway obstruction, not elsewhere specified). The demographic and clinical characteristics for the COPD subtype (Table 2) were similar to the overall COPD group (Table 1). Among patients with pre-existing chronic bronchitis, 36.68% had stage IV lung cancer compared with 40.23% in patients with pre-existing emphysema.

The overall median survival was longer in the Non-COPD group (206 days) compared to the COPD group (192 days; log rank $p<0.05$). When the data was stratified by stage, median survival decreased in the COPD group for each stage compared to the Non-COPD group [Figure 1] (stage I: 692 days vs 1130 days, $P<0.0001$; stage II: 473days vs 627 days, $P<0.0001$; stage III: 224 days vs 229 days; $P<0.0001$; stage IV: 106 days vs 112 days, $P<0.0001$). In the multivariate cox proportional hazard model, COPD patients exhibited 11% higher risk of death than Non-COPD patients (95% Confidence Interval (CI): 1.09—1.13) (Table 3). Increasing age, gender, race, comorbidity score, and

tumor grade were significantly associated with higher mortality risks. COPD patients were associated with elevated risk of death, decreasing with each stage of lung cancer as compared to Non-COPD group. Stage I patients had 39% higher risk of death (HR: 1.39, 95% CI: 1.33—1.46); Stage II patients had 20% higher risk of death (HR: 1.20, 95% CI: 1.11—1.30); Stage III patients had 9% higher risk of death (HR: 1.09, 95% CI: 1.05—1.32); and Stage IV patients had 4% higher risk of death (HR: 1.04, 95%CI: 1.02—1.07).

For COPD subtype, lung cancer patients with pre-existing chronic bronchitis had shorter median survival compared to emphysema across all stages of lung cancer [Figure 2] (stage I: 672 days vs 811 days, P<0.0001; stage II 582 days vs 445 days, P<0.0001; stage III: 255 days vs 229 days, P< 0.0001; stage IV: 105 days vs 112 days, P<0.0001). In the multivariate analysis, pre-existing chronic bronchitis was associated with a higher risk of death compared to the Non-COPD group and the differences between both groups decreased with each stage of lung cancer (Table 4). Stage I patients had 40% higher risk of death (HR: 1.40, 95% CI: 1.32—1.49); Stage II patients had 28% higher risk of death (HR: 1.28, 95% CI: 1.15—1.43); Stage III patients had 10% higher risk of death (HR: 1.10, 95% CI: 1.05—1.15); Stage IV had 6% higher risk of death (HR: 1.06, 95% CI: 1.02—1.10).

Patients with pre-existing emphysema also had higher risk of death compared to the Non-COPD group. However mortality risks for emphysema were lower than chronic bronchitis when compared to the Non-COPD group. Stage I patients had 22% higher risk of death (HR: 1.22, 95% CI: 1.11—1.35); Stage II patients had 7% higher risk of death (HR: 1.07, 95% CI: 1.02—1.28), Stage III patients had 2% higher risk of death (HR:

1.02, 95% CI: 1.01—1.08) and Stage IV patients had 1% higher risk of death (HR: 1.01, 95% CI: 0.91—1.06).

Discussion

Our study showed that elderly NSCLC patients with pre-existing COPD had shorter survival compared to the Non-COPD group. There were marked differences in early stage lung cancer, with a decrease in survival from stage I to stage IV in the COPD group compared to the Non-COPD group. Additionally, patients with chronic bronchitis subtype of COPD had shorter survival at every stage of lung cancer compared to emphysema.

One potential explanation for worse prognosis of lung cancer patients with COPD could be because of inadequate cancer treatments, poor pulmonary function, and lower quality of life. (17) Sekine et al found that the 5-yr survival rate of patients with COPD was significantly lower than the rate of patients with normal pulmonary function, because of a higher recurrence rate of tumors (77.0% versus 91.6%, respectively; $p<0.0001$). (18) Their study also suggested that the lung cancers developing in COPD patients tended to be higher grade malignancies, with well-differentiated adenocarcinoma. (18) Lopez-Encuentra et al highlighted that survival in stage I lung cancer patients after lung cancer surgery at 2 and 3 years was significantly worse in COPD patients than in Non-COPD patients. (19) Prior studies demonstrated that COPD was a significant risk factor for the development of respiratory-related complications and poorer long-term survival, because of respiratory failure after pulmonary resection for lung cancer. (20, 21) In the current

study, decreased time to death associated with pre-existing COPD, is consistent with the findings of these studies.

Several mechanisms have been proposed to explain the association between COPD and LC, including genetic risk factors (22), chronic local and systemic inflammatory processes (23), decreased immune surveillance (24), uncontrolled stimulation of bronchioalveolar stem cells (23), and common epigenetic processes, including oxidative stress leading to DNA damage, suppressed DNA repair and cellular proliferation (25). The association between COPD and lung cancer has been largely attributed to smoking history. (26) However, several lines of evidence suggest that the association between COPD and lung cancer may not be entirely due to smoking. Family history of chronic bronchitis and emphysema are associated with increased risk of lung cancer (27). In addition, COPD is associated with lung cancer in never-smokers. (28) A recent study estimated that COPD accounts for 10% of lung cancer cases among those who have never smoked and 12% among heavy smokers. (29) Among adenocarcinoma, which is more common among non-smokers, COPD remained strongly associated with lung cancer. (29)

Koshiol et al found that chronic bronchitis was most strongly associated with lung cancer among people who were diagnosed with chronic bronchitis more than 15 years prior to diagnosis of lung cancer. (30) Their study suggested that chronic bronchitis may act in an early stage of lung carcinogenesis is consistent with the findings of our study. One potential reason for increased risk of mortality among lung cancer patients with pre-existing chronic bronchitis could be chronic mucus hypersecretion (CMH). CMH is one of the cardinal features of chronic bronchitis. Prescott et al found that CMH increased

mortality risk related to lung function by 3.5 times. (31) CMH has been associated with lower forced expiratory volume 1, higher rates of hospitalizations, and a decline in lung health and quality of life. (32)

Studies have indicated that CMH and lung cancer may have some shared molecular pathology. (33, 34) Tesfaigzi et al demonstrated a significant association between CMH and the prevalence of altered DNA methylation of lung cancer-predictive genes in the sputum of smokers. The total methylation was higher in those with CMH than those without CMH. (35) Cilia motility plays a key role in clearing mucous from the lungs and is severely reduced in the COPD patient. Accumulating mucous may result in increased pulmonary inflammation and likely enhanced oxidative damage to DNA that in turn could play a role in further gene silencing through DNA hypermethylation. (36, 37) Altered DNA methylation of tumor suppressor genes promotes lung carcinogenesis. (35) Another study showed that epigenetic mediated silencing of tumor suppressor genes during development of COPD may contribute to the development of malignant NSCLC. (38)

Prior studies have established that cancer associated methylation of genes could be detected in sputum samples from high risk smokers prior to clinical diagnosis of lung cancer risk. (39, 40) Identification of these abnormalities in sputum samples from smokers with COPD may provide new biomarkers for COPD development and progression, and early cancer detection. (38) From our study, patients with pre-existing COPD had higher risk of mortality and decreased survival across all stages. Additionally, among COPD subtype, patients with pre-existing chronic bronchitis had highest risk of

mortality compared to emphysema and Non-COPD group. Screening for NSCLC in this population may have an excellent risk benefit ratio for early lung cancer detection.

The main strengths of the present study are the analysis of COPD subtype: chronic bronchitis and emphysema. As per our knowledge, the present study is the first in the literature that examined the impact of COPD subtype individually on elderly NSCLC. The study also has limitations. First, our results reflect Medicare populations of patients who are at least 66 years of age and above. Second, data on patients enrolled in health maintenance organizations (HMO) or fee-for-service plans was not available as HMOs are not required to submit claims to Medicare. Due to these reasons, the results of our study may not be generalizable to younger populations and patients enrolled in commercial insurance. Third, there is potential for misclassification of patients due to the use of ICD-9 coding errors in the data. Due to this, COPD may be under-represented and under-documented in our study. Fourth, information on factors such as smoking history, COPD disease severity, and health-related quality of life were not available in the data. We were therefore not able to assess the influence of these factors on survival.

Conclusion

These retrospective analyses illustrated the impact of pre-existing COPD and its subtypes: chronic bronchitis and emphysema on overall survival using a population-based, nationally validated claims dataset of patients over age 65, a group that is typically underrepresented in clinical trials. Elderly NSCLC patients with pre-existing COPD had shorter survival especially in the early stages of lung cancer, with a decrease in survival from Stage I to Stage IV. Among COPD subtypes, chronic bronchitis had shorter survival

at every stage of lung cancer compared to emphysema. Further research should include prospective cohort studies on COPD patients who develop lung cancer including COPD disease severity and smoking history.

References

1) What are the key statistics about lung cancer(2013), American Cancer Society. Retrieved from http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-key-statistics

2) Trends in COPD Morbidity and Mortality (2013). American Lung Association. Retrieved from http://www.lung.org/assets/documents/research/copd-trend-report.pdf

3) Centers for Disease Control and Prevention. National Center for Health Statistics: National Health Interview Survey Raw Data, 1997-2011. Analysis performed by American Lung Association Research and Health Education using SPSS and SUDAAN software.

4) Centers for Disease Control and Prevention. Chronic Obstructive Pulmonary Disease Surveillance — United States, 1971– 2000. Morbidity and Mortality Weekly Report. August 2, 2002; 51(SS06):1-16.

5) Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE; Lung Health Study Research Group. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med*. 2005; 142:233–239.

6)Young RP, Hopkins RJ, Christmas T, Black PN, Metcalf P, Gamble GD. COPD prevalence is increased in lung cancer, independent of age, sex and smoking history. *Eur Respir J*. 2009; 34(2):380-6.

7)Wasswa-Kintu S, Gan WQ, Man SFP, Pare PD, Sin DD. Relationship between reduced forced expiratory volume in one second and the risk of lung cancer: a systematic review and meta-analysis.*Thorax*. 2005;60:570–575.

8) Calabro E, Randi G, La Vecchia C, Sverzellati N, Marchiano A, Villani M et al. . Lung function predicts lung cancer risk in smokers: a tool for targeting screening programmes. *Eur Respir J*. 2010; 35(6):146-151.

9) Overview of the SEER Program. [cited April 8th 2011]; National Cancer Institute website]. Available from: http://seer.cancer.gov/about/overview.html.

10) Bray, F., & Parkin, D. M. (2009). Evaluation of data quality in the cancer registry: Principles and methods. part I: Comparability, validity and timeliness. *European Journal of Cancer, 45*(5), 747-755.

11) Centers for Medicare & Medicaid Services. (2012a). 2011 edition of the statistical supplement. Retrieved November 12, 2012, from http://www.cms.gov/ResearchStatistics-Data-and-Systems/Statistics-Trends-andReports/MedicareMedicaidStatSupp/2011.html

12) Potosky AL, Riley GF, Lubitz JD et al (1993) Potential for cancer related health services research using a linked Medicare-tumor registry database. Med Care 31:732–748

13) Simoni-Wastila, L., Keri Yang, H. W., Blanchette, C. M., Zhao, L., Qian, J., & Dalal, A. A. (2009). Hospital and emergency department utilization associated with treatment for chronic obstructive pulmonary disease in a managed-care Medicare population. *Current medical research and opinion*, *25*(11), 2729-2735.

14) Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemio l. 1992;45:613-9

15) Klabunde CN, Potosky AL, Legler JM, Warren JL. Development of a comorbidity index using physician claims data. J Clin Epidem iol. 2000;53:1258-67.

16) SEER-Medicare: Calculation of comorbidity weights [homepage on the Internet]. 2010. Available at: http://healthservices.cancer.gov/seermedicare/ program/comorbidity.html

17) Kurishima K, Satoh H, Ishikawa H, et al. Lung cancer patients with chronic obstructive pulmonary disease. Oncol Rep 2001; 8: 63–65.

18) Sekine, Y., Katsura, H., Koh, E., Hiroshima, K., & Fujisawa, T. (2012). Early detection of COPD is important for lung cancer surveillance. *European Respiratory Journal*, *39*(5), 1230-1240.

19) López-Encuentra, A., Astudillo, J., Cerezal, J., Gonzalez-Aragoneses, F., Novoa, N., & Sánchez-Palencia, A. (2005). Prognostic value of chronic obstructive pulmonary disease in 2994 cases of lung cancer. *European journal of cardio-thoracic surgery*, *27*(1), 8-13.

20) Sekine Y, Behnia M, Fujisawa T. Impact of COPD on pulmonary complications and on long-term survival of patients undergoing surgery for NSCLC. Lung Cancer 2002; 37: 95–101.

21) Namajika T, Sekine Y, Yamada Y, et al. Long-term surgical outcome in patients with lung cancer and coexisting severe COPD. Thorac Cardiovasc Surg 2009; 57: 339–342.

22) Young RP, Hopkins RJ, Gamble GD, Etzel C, El-Zein R, Crapo JD. Genetic evidence linking lung cancer and COPD: a new perspective. Appl Clin Genet 2011;4:99–111.

23) Houghton AM, Mouded M, Shapiro SD. Common origins of lung cancer and COPD. Nat Med 2008;14:1023–1024.

24) Rama I, Griny ´ o JM. Malignancy after renal transplantation: the role of immunosuppression. Nat Rev Nephrol 2010;6:511–519.

25) Bowman RV, Yang IA, Semmler AB, Fong KM. Epigenetics of lung cancer. Respirology 2006;11:355–365

26) Alberg AJ, Samet JM (2003) Epidemiology of lung cancer. Chest 123: 21S–49S

27) Gao Y, Goldstein AM, Consonni D, Pesatori AC, Wacholder S, et al. (2009) Family history of cancer and nonmalignant lung diseases as risk factors for lung cancer. Int J Cancer 125: 146–152.

28) Turner MC, Chen Y, Krewski D, Calle EE, Thun MJ (2007) Chronic obstructive pulmonary disease is associated with lung cancer mortality in a prospective study of never smokers. Am J Respir Crit Care Med 176: 285–290.

29) Yang P, Sun Z, Krowka MJ, Aubry MC, Bamlet WR, et al. (2008) Alpha1-antitrypsin deficiency carriers, tobacco smoke, chronic obstructive pulmonary disease, and lung cancer risk. Arch Intern Med 168: 1097–1103

30) Koshiol, J., Rotunno, M., Consonni, D., Pesatori, A. C., De Matteis, S., Goldstein, A. M., ... & Caporaso, N. E. (2009). Chronic obstructive pulmonary disease and altered risk of lung cancer in a population-based case-control study. *PLoS One*, *4*(10), e7380.

31) Prescott, E., Lange, P., & Vestbo, J. (1995). Chronic mucus hypersecretion in COPD and death from pulmonary infection. *European Respiratory Journal*, *8*(8), 1333-1338.

32) Tian, P. W., & Wen, F. Q. (2015). Clinical significance of airway mucus hypersecretion in chronic obstructive pulmonary disease. *Journal of Translational Internal Medicine*, *3*(3), 89-92.

33) Brenner DR, McLaughlin JR, Hung RJ: Previous lung diseases and lung cancer risk: a systematic review and meta-analysis. PLoS One 2011, 6:e17479.

34) Wang H, Yang L, Zou L, Huang D, Guo Y, Pan M, Tan Y, Zhong H, Ji W, Ran P, et al: Association between Chronic Obstructive Pulmonary Disease and

Lung Cancer: A Case–control Study in Southern Chinese and a MetaAnalysis. PLoS One 2012, 7:e46144

35) Bruse, S., Petersen, H., Weissfeld, J., Picchi, M., Willink, R., Do, K., ... & Tesfaigzi, Y. (2014). Increased methylation of lung cancer-associated genes in sputum DNA of former smokers with chronic mucous hypersecretion. *Respiratory research*, *15*(1), 2.

36) Leng S, Stidley CA, Willink R, et al. Double-strand break damage and associated DNA repair genes predispose smokers to gene methylation. Cancer Res. 2008; 68:3049–3056.

37) Cuozzo C, Porcellini A, Angrisano T, et al. DNA damage, homology-directed repair, and DNA methylation. PLoS Genet. 2007; 3:e110

38) Tessema, M., Yingling, C. M., Picchi, M. A., Wu, G., Liu, Y., Weissfeld, J. L., ... & Belinsky, S. A. (2015). Epigenetic repression of CCDC37 and MAP1B links chronic obstructive pulmonary disease to lung cancer. *Journal of Thoracic Oncology*, *10*(8), 1181-1188.

39) de Oca MM, Halbert RJ, Lopez MV, Perez-Padilla R, Tálamo C, Moreno D, et al. The chronic bronchitis phenotype in subjects with and without COPD: the PLATINO study. Eur Respir J. 2012;40:28–36.

40) Burgel PR, Nesme-Meyer P, Chanez P, Caillaud D, Carre P, Perez T, et al. Cough and sputum production are associated with frequent exacerbations and hospitalizations in COPD subjects. Chest. 2009;135:975–82.

Table 1a. Characteristics of NSCLC patients with and without COPD

Covariate	COPD (%)	No COPD (%)	Total (%)	p value
No of patients	22,497 (33.60)	44,466 (66.40)	66,963	
Sex				0.1463
Males	11,626 (51.68)	22,715 (51.08)	34,341 (51.28)	
Females	10,871 (48.32)	21,751 (48.92)	32,622 (48.72)	
Race				<0.0001
White	20,414 (90.74)	38,447 (86.46)	58,861 (87.90)	
Black	1510 (6.71)	3692 (8.30)	5202 (7.77)	
American Indian	65 (0.29)	126 (0.28)	191 (0.29)	
Asian	472 (2.09)	2128 (4.79)	2600 (3.88)	
Other	36 (0.16)	73 (0.16)	109 (0.16)	
Age Mean (SD)	74.73 (6.39)	75.42 (6.94)		<0.0001
Age Group (yr)				<0.0001
66-69	4887 (21.72)	9461 (21.28)	14,348 (21.43)	
70-73	4731 (21.03)	8429 (18.96)	13,160 (19.65)	
74-79	6586 (29.28)	12,389 (27.86)	18,975 (28.34)	
80+	6293 (27.97)	14,187 (31.91)	20,480 (30.58)	
Comorbidities				
Myocardial Infarction	802 (3.56)	1878 (4.22)	2680 (4.0)	<0.0001
Congestive Heart Failure	2587 (11.50)	3829 (8.61)	6416 (9.58)	<0.0001
Peripheral Vascular Disease	1393 (6.19)	2014 (4.53)	3407 (5.09)	<0.0001
Cerebrovascular Disease	1002 (4.45)	2263 (5.09)	3265 (4.88)	0.0003
Dementia	214 (0.95)	650 (1.46)	864 (1.29)	<0.0001
Asthma	468 (2.08)	1287 (2.98)	1755 (2.62)	<0.0001
Connective Tissue Disease	306 (1.36)	643 (1.45)	949 (1.42)	0.3746
Peptic Ulcer	196 (0.87)	419 (0.94)	615 (0.92)	0.3625
Mild Liver Disease	184 (0.82)	529 (1.19)	713 (1.06)	<0.0001
Diabetes Mellitus	2355 (10.47)	5207 (11.71)	7562 (11.29)	<0.0001
Diabetes with complications	187 (0.83)	366 (0.82)	553 (0.83)	<0.9127
Hemiplegia	73 (0.32)	373 (0.84)	446 (0.67)	<0.0001

Table 1a (Continued)

Renal Disease	837 (3.72)	1713 (3.85)	2550 (3.81)	0.3997
Severe Liver Disease	34 (0.15)	130 (0.29)	164 (0.24)	0.0005
AIDS	4 (0.02)	17 (0.04)	21 (0.03)	0.158
Charlson's Comorbidity Score				0.016
0 to 2	21,545 (95.77)	42,785 (96.22)	64,330 (96.07)	
3 to 5	932 (4.14)	1650 (3.71)	2582 (3.86)	
>5	20 (0.09)	31 (0.07)	51 (0.08)	
Tumor Grade				<0.0001
Well differentiated	716 (3.18)	1847 (4.15)	2563 (3.83)	
Moderately differentiated	3093 (13.75)	6122 (13.77)	9215 (13.76)	
Poorly differentiated	5007 (22.26)	9665 (21.74)	14,672 (21.91)	
Undifferentiated	1127 (5.01)	2126 (4.78)	3253 (4.86)	
Unknown	12,554 (55.80)	24,706 (55.56)	37,260 (55.64)	
Stage				<0.0001
Localised	5078 (22.63)	7401 (16.67)	12,479 (18.67)	
Regional	5251 (23.40)	9195 (20.71)	14,446 (21.61)	
Metastatic	10,398 (46.33)	24,569 (55.33)	34,967 (52.31)	
Unstaged	181 (0.80)	503 (1.13)	564 (0.84)	
Not Applicable	1589 (7.08)	2798 (6.30)	1589 (7.08)	
Stage (TNM)				<0.0001
Stage I	4835 (21.49)	7184 (16.16)	12,019 (17.95)	
Stage II	1123 (4.99)	2282 (5.13)	3405 (5.08)	
Stage IIIA	1977 (8.79)	3417 (7.68)	5394 (8.06)	
Stage IIIB	3338 (14.84)	6680 (15.02)	10,018 (14.96)	
Stage IV	8176 (36.34)	19,675 (44.25)	27,851 (41.59)	
Unknown	3048 (13.55)	5228 (11.76)	8276 (12.36)	

Table 1b. Characteristics of NSCLC patients with pre-existing COPD by COPD subtype

Covariate	Chronic Bronchitis (%)	Emphysema (%)	No COPD (%)	Total (%)	P-value
No of patients	11,221 (18.97)	3475 (5.87)	44,466 (75.15)	59,162	
Sex					0.45
Males	5809 (51.77)	1787 (51.42)	22,715 (51.08)	30311 (51.23)	
Females	5412 (48.23)	1688 (48.58)	21,751 (48.92)	28,851 (48.76)	
Race					<0.0001
White	10,315 (91.93)	3024 (87.02)	38,447 (86.46)	51,786 (87.53)	
Black	720 (6.42)	343 (9.87)	3692 (8.30)	4755 (8.03)	
American Indian	36 (0.32)	3 (0.09)	126 (0.28)	165 (0.27)	
Asian	137 (1.22)	96 (2.76)	2128 (4.79)	2361 (3.99)	
Other	13 (0.12)	9 (0.26)	73 (0.16)	95 (0.16)	
Age Mean (SD)	74.73 (6.39)	74.71 (6.35)	75.42 (6.94)		<0.0001
Age Group (yr)					<0.0001
66-69	2449 (21.83)	743 (21.38)	9461 (21.28)	12653 (21.38)	
70-73	2411 (21.49)	633 (18.22)	8429 (18.96)	11473 (19.39)	
74-79	3314 (29.53)	1098 (31.60)	12,389 (27.86)	16801 (28.39)	
80+	3047 (27.15)	1001 (28.81)	14,187 (31.91)	18,235 (30.82)	
Comorbidities					
Myocardial Infarction	410 (3.65)	143 (4.12)	1878 (4.22)	2431(4.10)	0.027
Congestive Heart Failure	1527 (13.61)	344 (9.90)	3829 (8.61)	5700 (9.63)	<0.0001

Table 1b (Continued)

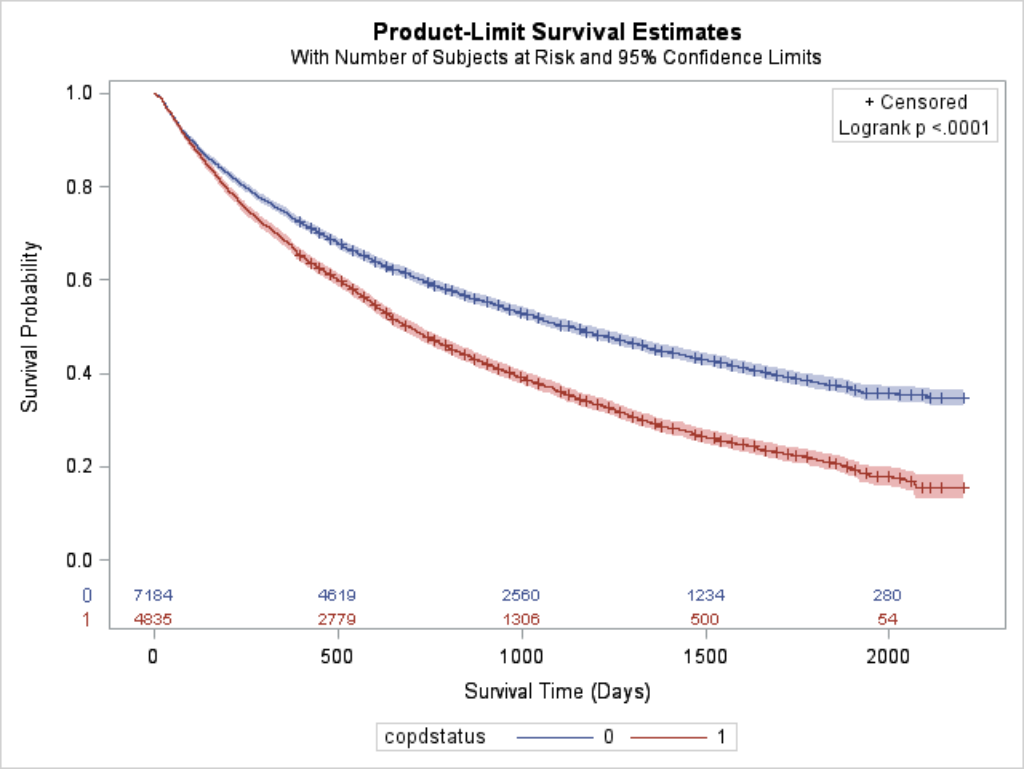
Peripheral Vascular Disease	599 (5.34)	202 (5.81)	2014 (4.53)	2815 (4.75)	<0.0001
Cerebrovascular Disease	445 (3.97)	162 (4.66)	2263 (5.09)	2870 (4.85)	<0.0001
Dementia	104 (0.93)	27 (0.78)	650 (1.46)	781 (1.32)	<0.0001
Asthma	278 (2.48)	110 (3.17)	1287 (2.98)	1675 (2.83)	0.03
Connective Tissue Disease	132 (1.18)	48 (1.38)	643 (1.45)	823 (1.39)	0.09
Peptic Ulcer	89 (0.79)	29 (0.83)	419 (0.94)	537 (0.90)	0.31
Mild Liver Disease	81 (0.72)	29 (0.83)	529 (1.19)	639 (1.09)	<0.0001
Diabetes uncomplicated	1170 (10.43)	320 (9.21)	5207 (11.71)	6697 (11.31)	<0.0001
Diabetes complicated	85 (0.76)	30 (0.86)	366 (0.82)	481 (0.81)	0.76
Hemiplegia	49 (0.44)	18 (0.52)	373 (0.84)	440 (0.74)	<0.0001
Renal Disease	486 (4.33)	127 (3.65)	1713 (3.85)	2326 (3.93)	0.04
Severe Liver Disease	19 (0.17)	3 (0.09)	130 (0.29)	152 (0.25)	0.009
AIDS	0	0	17 (0.04)	17 (0.02)	0.06
Charlson's Comorbidity Score					<0.0001
0 to 2	10,686 (95.23)	3316 (95.42)	42,785 (96.22)	56,787 (95.98)	
3 to 5	529 (4.71)	155 (4.46)	1650 (3.71)	2334 (3.94)	
>5	6 (0.05)	4 (0.12)	31 (0.07)	41 (0.06)	

Table 1b (Continued)

Tumor Grade					<0.0001
Well differentiated	340 (3.03)	147 (4.23)	1847 (4.15)	2334 (3.94)	
Moderately differentiated	1476 (13.15)	529 (15.22)	6122 (13.77)	8127 (13.73)	
Poorly differentiated	2420 (21.57)	789 (22.71)	9665 (21.74)	12,874 (21.76)	
Undifferentiated	567 (5.05)	182 (5.24)	2126 (4.78)	2,875 (4.85)	
Unknown	6418 (57.19)	1828 (52.61)	12,554 (55.80)	20,800 (35.15)	
Stage					<0.0001
Localised	2491 (22.26)	760 (21.94)	7401 (16.67)	10,652 (18.0)	
Regional	2585 (23.10)	786 (22.69)	9195 (20.71)	12,566 (21.23)	
Metastatic	5315 (47.48)	1731 (49.97)	24,569 (55.33)	31,615 (53.43)	
Unstaged	99 (0.88)	36 (1.03)	438 (0.99)	573 (0.96)	
Not Applicable	733 (6.55)	162 (4.68)	2798 (6.30)	3693 (6.24)	
Stage (TNM)					<0.0001
Stage I	2402 (21.41)	766 (22.04)	7184 (16.16)	10,352 (17.49)	
Stage II	539 (4.80)	171 (4.92)	2282 (5.13)	2992 (5.05)	
Stage IIIA	986 (8.79)	284 (8.17)	3417 (7.68)	4687 (7.92)	
Stage IIIB	1731 (15.43)	505 (14.53)	6680 (15.02)	8916 (15.07)	
Stage IV	4116 (36.68)	1398 (40.23)	19,675 (44.25)	25,189 (42.57)	
Unknown	1447 (12.90)	351 (10.10)	5228 (11.76)	7026 (11.87)	

Figure 1: Kaplan Meier Survival Analysis of COPD versus Non-COPD among NSCLC Patients

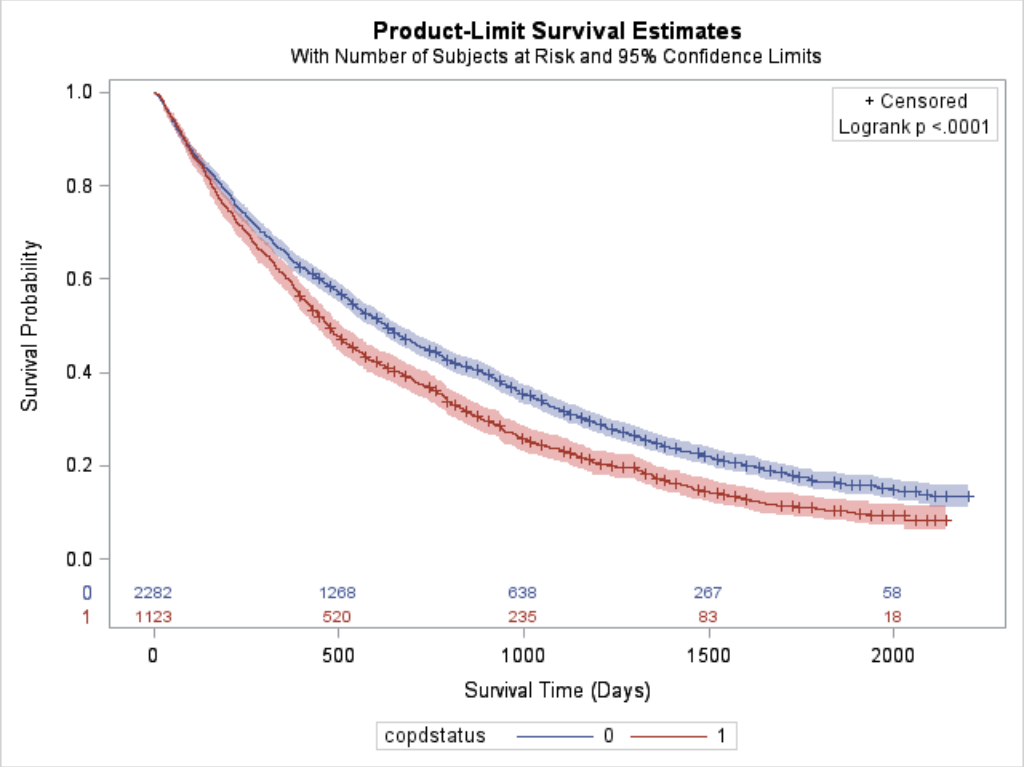
Stage I NSCLC



Group	Total	Dead	Alive Censored	Percent Alive	Median (Days)
NonCOPD(0)	7184	3726	3458	48.13	1130
COPD(1)	4835	3220	1615	33.4	692

Figure 1 (Continued)

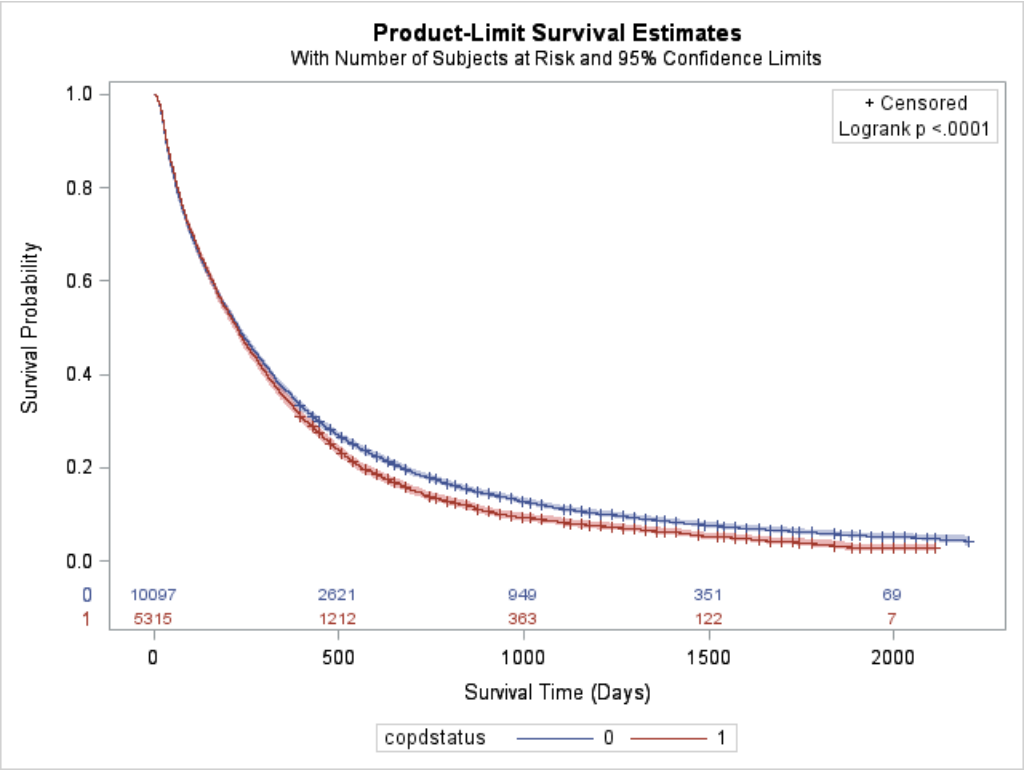
Stage II NSCLC



Group	Total	Dead	Alive Censored	Percent Alive	Median (Days)
NonCOPD(0)	2282	1701	581	25.46	627
COPD(1)	1123	916	207	18.43	473

Figure 1 (Continued)

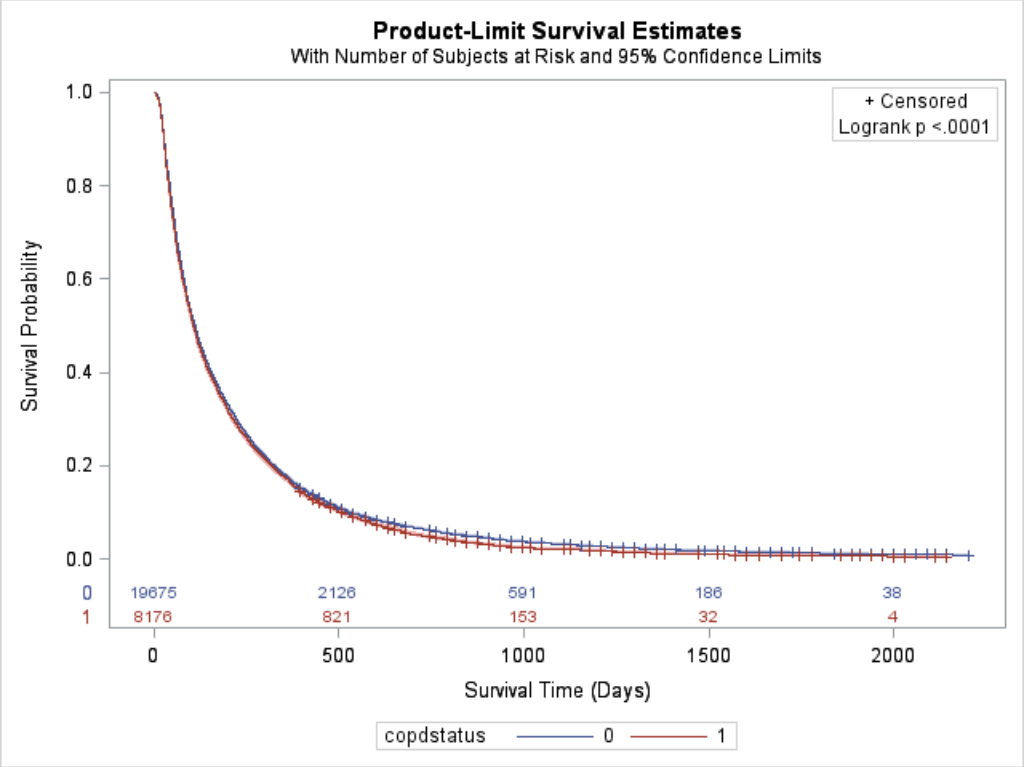
Stage III NSCLC



Group	Total	Dead	Alive Censored	Percent Alive	Median (Days)
NonCOPD(0)	10097	9029	1068	10.58	255
COPD(1)	5315	4889	426	8.02	224

Figure 1 (Continued)

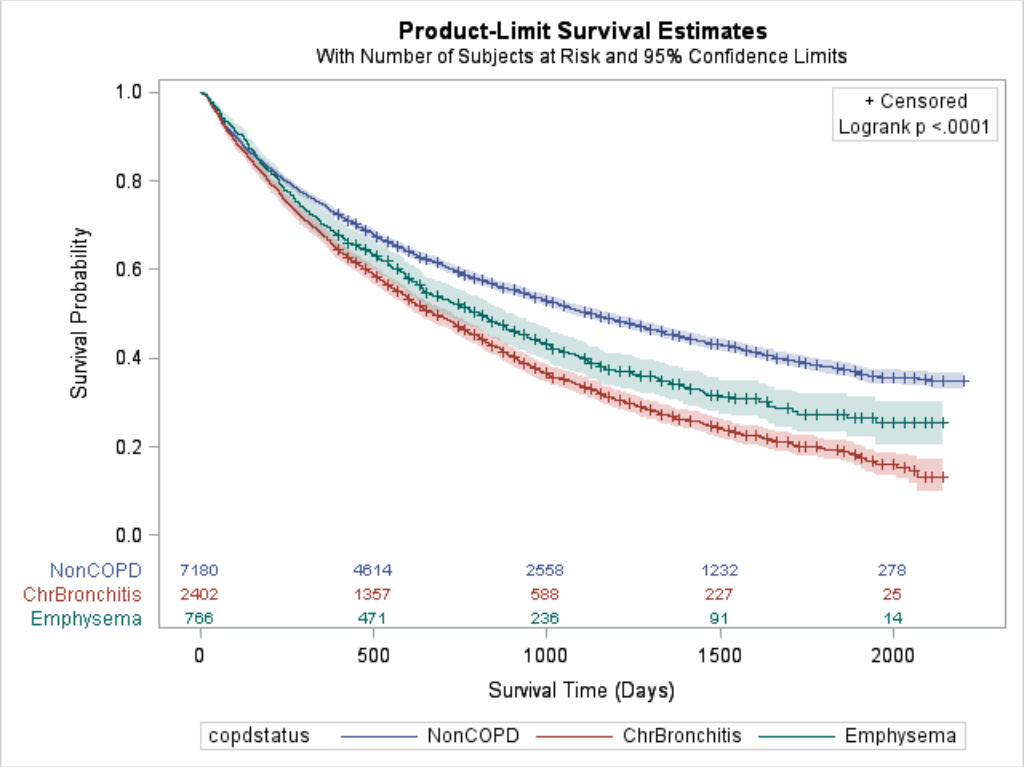
Stage IV NSCLC



Group	Total	Dead	Alive Censored	Percent Alive	Median (Days)
NonCOPD(0)	19675	19134	541	2.75	112
COPD(1)	8176	8003	173	2.12	106

Figure 2: Kaplan Meier Survival Analysis of COPD subtype: chronic bronchitis versus emphysema versus Non-COPD among NSCLC Patients

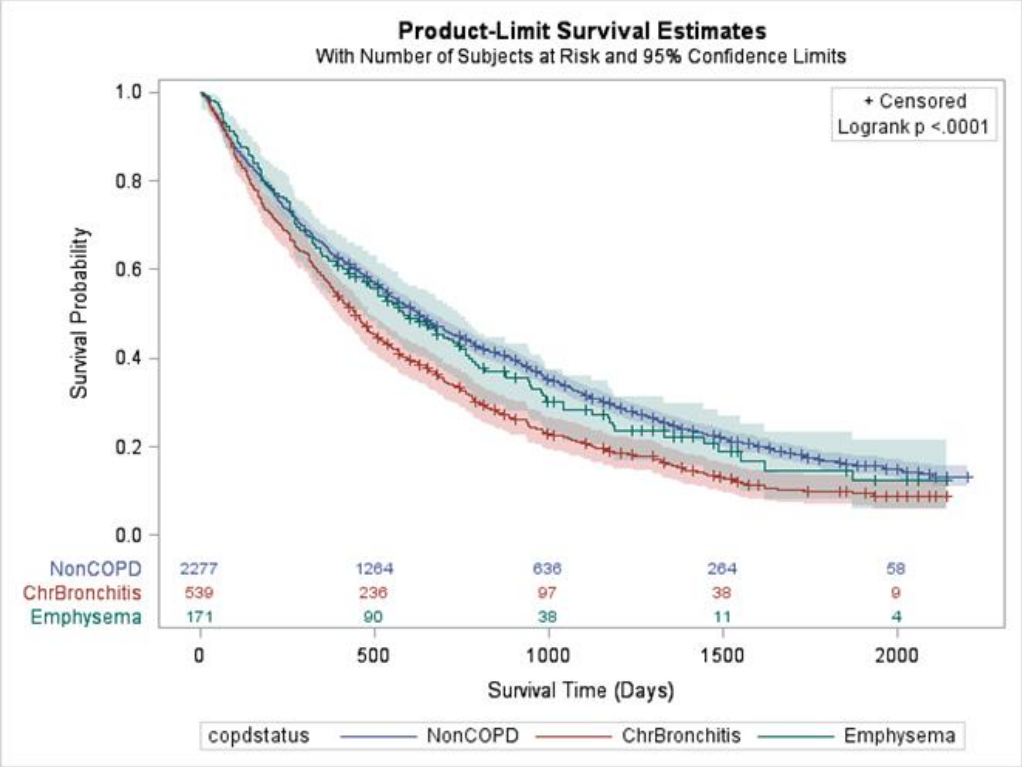
Stage I NSCLC



Group	Total	Dead	Alive Censored	Percent Alive	Median (Days)
NonCOPD	7184	3726	3458	48.13	1130
Emphysema	766	473	293	38.25	811
Chr Bronchitis	2402	1640	762	31.72	672

Figure 2 (Continued)

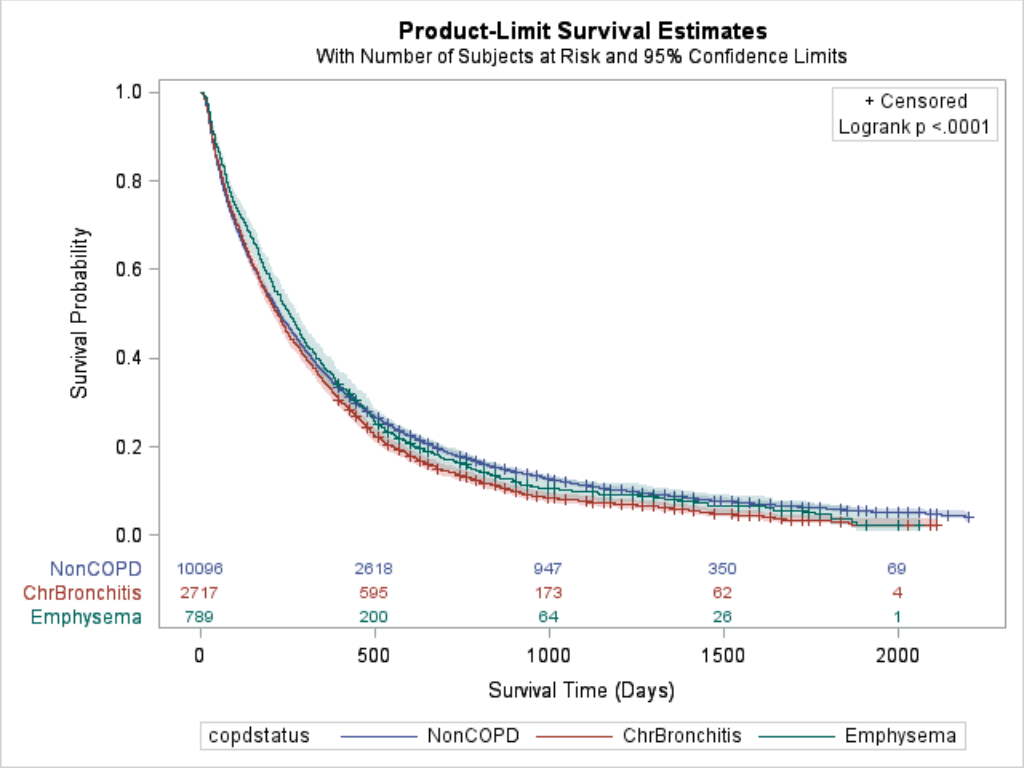
Stage II NSCLC



Group	Total	Dead	Alive Censored	Percent Alive	Median (Days)
NonCOPD	2282	1701	581	25.46	627
Emphysema	171	125	46	26.9	582
Chr Bronchitis	539	446	93	17.25	445

Figure 2 (Continued)

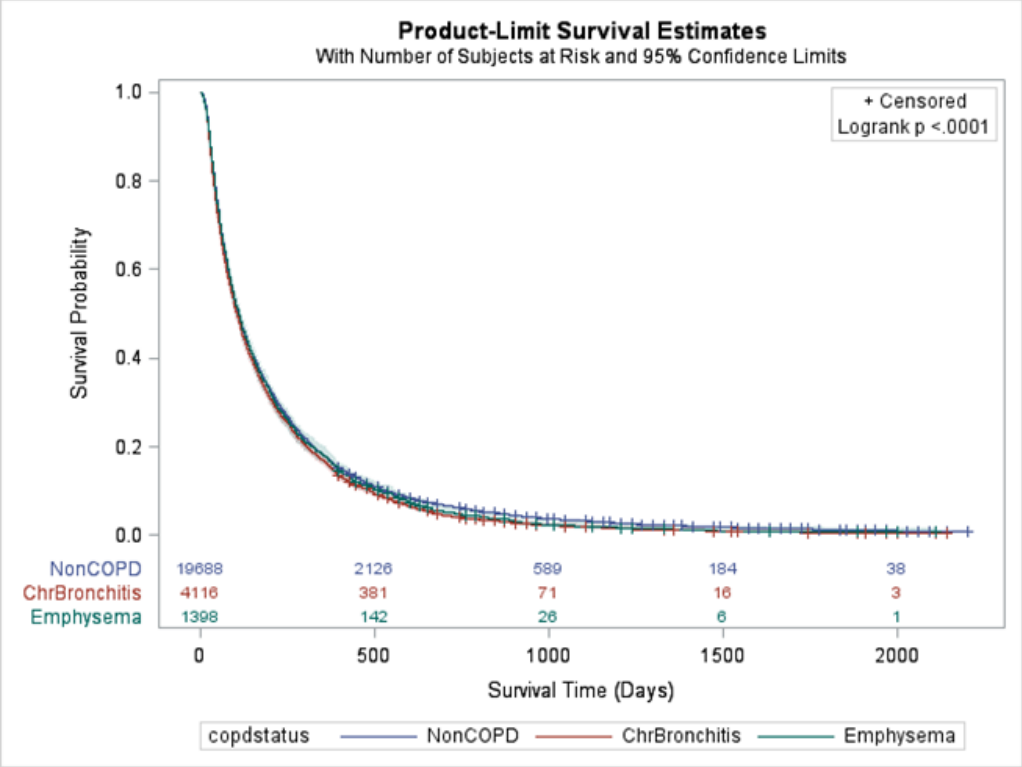
Stage III NSCLC



Group	Total	Dead	Alive Censored	Percent Alive	Median (Days)
NonCOPD	10097	9029	1068	10.58	255
Emphysema	789	719	70	8.87	229
Chr Bronchitis	2717	2522	195	7.18	222

Figure 2 (Continued)

Stage IV NSCLC



Group	Total	Dead	Alive Censored	Percent Alive	Median (Days)
NonCOPD	19675	19134	541	2.75	112
Emphysema	1398	1365	33	2.36	110
Chr Bronchitis	4116	4041	75	1.82	105

Table 1c: *Cox Proportional Hazard Model for COPD versus Non-COPD among NSCLC patients

Stage	HR	LCI	UCI
ALL	1.11	1.09	1.13
Stage I	1.39	1.33	1.46
Stage II	1.2	1.11	1.3
Stage III	1.09	1.05	1.32
Stage IV	1.04	1.02	1.07

$p<0.0001$
Non COPD=Reference
*Adjusted for Covariates
HR= Hazard Ratio
LCI= Lower Confidence Interval
UCI= Upper Confidence Interval

Table 1d: *Cox Proportional Hazard Model for COPD subtypes among NSCLC patients

Stage	HR	LCI	UCI
All			
Chronic Bronchitis	1.13	1.11	1.16
Emphysema	1.03	1.01	1.07
Stage I			
Chronic Bronchitis	1.4	1.32	1.49
Emphysema	1.22	1.11	1.35
Stage II			
Chronic Bronchitis	1.28	1.15	1.43
Emphysema	1.07	1.02	1.28
Stage III			
Chronic Bronchitis	1.1	1.05	1.15
Emphysema	1.02	1.01	1.08
Stage IV			
Chronic Bronchitis	1.06	1.02	1.1
Emphysema	1.01	0.91	1.06

$p<0.0001$

Non COPD=Reference

*Adjusted for Covariates

HR= Hazard Ratio

LCI= Lower Confidence Interval

UCI= Upper Confidence Interval

CHAPTER 3: CACHEXIA ASSOCIATED WITH COPD AMONG NSCLC

Introduction

Lung cancer and chronic obstructive pulmonary disease (COPD) are among leading causes of morbidity and mortality worldwide. Lung cancer is the second most common cancer in both men and women. The American Cancer Society estimates 224,390 new cases of lung cancer in the United States (US) in 2016. (1) According to the American Lung Association, COPD is the third leading cause of death in the US after cancer and heart disease. In 2010, COPD accounted for 134,676 deaths in the US. (2) About 15--40% of patients with COPD experience muscle wasting depending on the stage of the disease. (3) Prior studies have shown that muscle wasting not only contributes to diminished skeletal muscle function, reduced exercise capacity, and decreased health status, (4, 5) but is also a determinant of mortality in COPD, independent of airflow obstruction. (6, 7)

Cancer Cachexia is also known as cancer anorexia-cachexia. It is a combination of both starvation caused by anorexia and wasting syndrome due to cachexia. (8) It is a debilitating condition characterized by involuntary loss of weight, muscle wasting, and loss of appetite. (9) Patients suffering from cancer cachexia have a poor quality of life, and experience pain and fatigue. Moreover, among cancer patients, cachexia contributes to poor response to chemotherapy and poor surgical and clinical outcomes. (9)

In advanced stages of cancer, cachexia cannot be cured by increasing food intake or nutritional supplements. (10)

Cachexia affects most patients with advanced cancer and the prevalence of cancer anorexia-cachexia depends on the type of cancer. (11) Vaughan et al highlighted that 50% to 85% of patients with gastrointestinal, pancreatic, lung, and colorectal cancer have weight loss at the time of cancer diagnosis and before treatment. (12) In the United States, it is estimated that more than 1.3 million people have cancer anorexia-cachexia. Moreover, cancer cachexia is responsible for 20% of all cancer deaths, contributing to more than 7.4 million deaths worldwide each year.(13) In industrialized countries (North America, Europe, Japan), the overall prevalence of cachexia (due to any disease) is growing and currently about 1%, i.e., about nine million patients.(11)

Suzuki et al estimated that more than 20% of cancer patients died due to cachexia, and more than 50% of patients died with cachexia.(14) In another study by Bennanl-Balti N et al, patients indicated that their quality of life was affected more by weight loss and poor nutritional status than by the cancer itself. (15) Cachexia affects majority of cancer patients and therefore poses significant burden on the patients as well as the healthcare system.

Approximately 10% of patients diagnosed with NSCLC die from cancer cachexia. (11) Cachexia is associated with a continuum starting at pre-cachexia stage through refractory cachexia with the possibility of reversibility in the pre-cachexia stage. (16) A more thorough understanding of the pathophysiology of cachexia development and progression is needed that will likely guide treatment approaches. Moreover, no studies have examined the onset of cachexia among elderly COPD patients with NSCLC. We

examined the onset of cachexia in NSCLC patients with and without pre-existing COPD. Information on determining the onset of cachexia during lung cancer would help in early detection and intervention of this wasting syndrome.

Methods

Patients were identified from the linkage of two data sources, the Surveillance, Epidemiology, and End Results (SEER) program database from the National Cancer Institute and the Medicare enrollment and claims files from the Centers for Medicare and Medicaid Services. The SEER system of population-based cancer registries covers approximately 28% of the US population spanning 18 geographically defined areas. The SEER program collects information which includes patient demographics, tumor characteristics, stage, and survival status. (17)

All incident cancer patients reported to the SEER registries are cross-matched with a master file of Medicare enrollment. (18) All Medicare beneficiaries receive Part A coverage (inpatient care, skilled nursing, home health care, and hospice care). Approximately 95 % of beneficiaries subscribe to Part B, which covers physician services and outpatient care. The SEER-Medicare linkage included all Medicare eligible persons appearing in the SEER data and their Medicare claims for Part A (inpatient) and Part B (outpatient and physician services). (19)

We identified patients diagnosed with NSCLC between 2005 and 2010. We included patients aged 66 years or older and continuously enrolled in Medicare Parts A and B in the 12 months prior to diagnosis. Patients were excluded if diagnosis was made at autopsy, death certificate, or in an unknown month, or if their date of death was

recorded prior to or the same month as diagnosis, and if they were enrolled in a health maintenance organization (HMO) at any time during the 12 months prior to diagnosis. NSCLC diagnosis was based on the International Classification of Disease for Oncology (3rd edition, ICD-O-3) histology codes in the SEER data. Tumor stage was classified according to the sixth edition of the American Joint Commission on Cancer manual for patients diagnosed between 2005 to 2010. The diagnosis of COPD prior to cancer diagnosis was determined using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes (491 [chronic bronchitis], 492 [emphysema], 496 [chronic airway obstruction, not elsewhere classified]) in the Medicare claim files. (20) Similarly, Cachexia in NSCLC patients were also identified using ICD-9-CM codes (799.4, 783.21, 783.22, 783.0). (21)

We identified 15 non-cancer comorbidities from the Charlson Comorbidity Index using Medicare claim files. Descriptive statistics were used to summarize demographic and clinical characteristics of NSCLC patients by COPD status (COPD vs. Non COPD). Chi-square test for categorical variables and t-tests for continuous variables determined differences between groups. Time to cachexia was measured from lung cancer diagnosis date to cachexia diagnosis date. Patients who did not develop cachexia were considered as censored. Kaplan Meier method and corresponding log-rank tests were used to examine overall time to occurrence of cachexia by COPD status. Statistical significance was established at $P <= 0.05$. SAS 9.4 (SAS Institute Inc, Cary, North Carolina) was used for all data analyses.

Results

Based on the inclusion and exclusion criteria, we identified 66,963 NSCLC patients. Of these, 22,497 (33.60%) had COPD prior to NSCLC diagnosis. Table 1 shows the distribution of clinical and demographic characteristics between pre-existing COPD and Non-COPD lung cancer patients. The mean age of all patients in the study was 75 years. Majority of patients in the COPD (51.68%) and Non-COPD (51.08%) group were males. Caucasians accounted for the greatest proportion of lung cancer patients in both groups (90.74% and 86.46% respectively) followed by African-Americans (6.71% and 8.30%). The most common comorbid conditions among COPD and Non-COPD groups were congestive heart failure (11.50% and 8.61%), diabetes mellitus (10.47% and 11.71%), peripheral vascular disease (6.19% and 4.53%) and cerebrovascular disease (4.45% and 5.09%). The comorbidity status of both groups, measured by the Charlson's Comorbidity Index (CCI), was statistically significant.

Nearly all COPD and Non-COPD patients (approximately 99%) had invasive tumors. Approximately 22% of COPD patients had poorly differentiated tumor grade compared with 21% of patients in the Non-COPD group. Majority of lung cancer patients among COPD and Non-COPD groups were diagnosed with stage IV cancer (36.34% and 44.25%).

A total of 1437 NSCLC patients were identified with cachexia across the study. Among these, 185 (0.82%) were in the COPD group and 1252 (2.82%) were in the Non-COPD group (Table 2). Stage IV NSCLC patients accounted for the highest proportion of cachectic patients among COPD (1.04%) and Non-COPD (3.19%) groups.

The median time to cachexia in NSCLC patients by COPD status could not be determined as approximately 98% of the observations were censored.

Discussion

Among 66,963 patients diagnosed with NSCLC in the SEER-Medicare data, only 1437 (2.14%) patients had documented comorbid cachexia. These finding are similar to the study by Fox et al. In a retrospective study of more than 8500 cancer patients, Fox et al (22) estimated the proportion of cachexia patients using four different definitions based on two sets of ICD-9 codes, prescriptions for appetite stimulants or documented weight loss ≥5%. The two sets of ICD-9 codes were i) ICD-9 code for cachexia (799.4), ii) ICD-9 code for cachexia, anorexia (783.0), abnormal weight loss (783.21), and feeding difficulties (783.22). The proportion assigned a diagnosis of documented cachexia varying from 2% (ICD-9 code 799.4), 5.5% (ICD-9 799.4, 783.0, 783.21, 783.22), to 15% based on weight loss ≥5%. Their study demonstrated that the proportion of patients with cachexia varied depending upon the definition employed.

Even though 60% to 80% of patients with cancer suffer from significant weight loss (23), the current study as well as Fox et al identified a very small proportion of patients with documented cancer cachexia. Due to the small proportion of cachectic lung cancer patients in our study, we could not perform survival analysis to estimate time to cachexia. These studies indicate that cachexia is underestimated and under-documented by the healthcare community. The possible underestimation of cachexia could be due to several factors including lack of screening protocols, absence of weight loss data prior to cancer diagnosis, and standardized diagnostic criteria. (24)

About 25% to 40% of COPD patients experience pulmonary cachexia (25, 26) associated with approximately 50% reduction in median survival. (27) The pathogenetic mechanism for cachexia among COPD patients has been suggested to result from energy imbalance, disuse atrophy of muscles, hypoxemia, systemic inflammation, hormonal insufficiency, and accelerated ageing. (27) The mechanism of cachexia among lung cancer patients involves multiple pathways including procachetic and proinflammatory signals from tumor cells, systemic inflammation in the host, increased energy expenditure, and alterations of protein, fat, and carbohydrate metabolism. These changes lead to skeletal muscle and adipose tissue loss resulting in substantial loss of body weight and lean muscle mass. (28) ICD-9 codes for cachexia may not capture the loss of body weight and lean muscle mass based on the pathophysiology of cancer and pulmonary cachexia.

Research in cachexia has been challenging due to the absence of a universally accepted definition of cachexia. Moreover, the average age of a lung cancer patient is generally between 65 to 75 years. (28) Elderly patients are especially at risk and more vulnerable to varying degrees of age-related sarcopenia irrespective of other co-morbidities (such as heart failure, chronic renal failure and chronic obstructive pulmonary disease) that can compound cancer-related muscle wasting. (29) Anecdotal evidence indicates that physicians may diagnose abnormal weight loss among their cancer patients however they may not code for billing purposes. Physicians may not include abnormal weight loss in the diagnostic codes for billing as they do not receive any additional reimbursement for patients with abnormal weight loss. Therefore abnormal weight loss may not appear in claims databases. Moreover, diagnostic codes for cachexia may be

used more frequently towards the end of life when there are visual signs of wasting as opposed to earlier diagnosis when the course of the disease can be altered through appropriate treatments. (21)

As cachexia is a syndrome, defining cachexia has been a challenge due to multiple definitions in the literature. In 2011, an international consensus statement on cancer cachexia highlighted three diagnostic criteria: (1) unintentional weight loss (>5% over past 6 months in absence of simple starvation); (2) weight loss >2% when BMI was <20 kg/m^2; and (3) appendicular skeletal muscle index consistent with sarcopenia and any weight loss > 2%. (30) Fearon et al proposed the concept of a continuous spectrum of cancer cachexia development involving precachexia, cachexia, and refractory phase. (30) Diagnostic criteria should be both sensitive and specific to be of value in clinical practice. It is therefore important to validate these and emerging definitions of cachexia.

Studies have highlighted that cachexia is reversible in patients who have not reached the refractory stage. (30, 31) Early recognition of cachexia is therefore important so that patients can be selected for multimodal treatment programs. Knowledge and awareness of this underrepresented condition will enable physicians to identify, diagnose, and treat all cases of cachexia. It will also aid in characterizing the burden of cancer-cachexia in terms of mortality, health-related quality of life, and healthcare resource utilization.

Conclusion

Refinement of diagnostic criteria as well as large contemporary datasets with cachexia diagnostic criteria and clinical outcomes is necessary for further research on cachexia among lung cancer patients.

References

1) What are the key statistics about lung cancer(2013), American Cancer Society. Retrieved from http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-key-statistics

2) Trends in COPD Morbidity and Mortality (2013). American Lung Association. Retrieved from http://www.lung.org/assets/documents/research/copd-trend-report.pdf

3) Schols AM, Soeters PB, Dingemans AM, Mostert R, Frantzen PJ, Wouters EF. Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. Am Rev Respir Dis 1993;147:1151–1156.

4) Mostert R, Goris A, Weling-Scheepers C, Wouters EF, Schols AM. Tissue depletion and health related quality of life in patients with chronic obstructive pulmonary disease. Respir Med 2000;94:859–867.

5) Engelen MP, Schols AM, Baken WC, Wesseling GJ, Wouters EF. Nutritional depletion in relation to respiratory and peripheral skeletal muscle function in out-patients with COPD. Eur Respir J 1994;7:1793–1797.

6) Vestbo J, Prescott E, Almdal T, Dahl M, Nordestgaard BG, Andersen T, et al. Body mass, fat-free body mass, and prognosis in patients with chronic obstructive pulmonary disease from a random population sample: findings from the Copenhagen City Heart Study. Am J Respir Crit Care Med 2006;173:79–83.

7) Schols AM, Broekhuizen R, Weling-Scheepers CA, Wouters EF. Body composition and mortality in chronic obstructive pulmonary disease. Am J Clin Nutr 2005;82:53–59.

8) Fearon K et al., Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol*2011;12:489–95.

9) Benner A et al., Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol*2013;10:90–9.

10) Bennani-Baiti N et al., What is cancer anorexia-cachexia syndrome? A historical perspective. *J R Coll Physicians Edinb* 2009;39:257–62.

11) von Haehling S et al., Cachexia as a major underestimated and unmet medical need: facts and numbers. *J Cachexia Sarcopenia Muscle* 2010;1:1–5.

12) Vaughan VC et al., Cancer cachexia: impact, mechanisms and emerging treatments. *J Cachexia Sarcopenia Muscle* 2013;4:95–109

13) Dodson S, et al., Muscle wasting in cancer cachexia: clinical implications, diagnosis, and emerging treatment strategies. Annu Rev Med 2011;62:265–79.

14) Suzuki H et al., Cancer cachexia-pathophysiology and management. *J Gastroenterol* 2013;48:574–594.

15) Bennani-Baiti N et al., What is cancer anorexia-cachexia syndrome? A historical perspective. *J R Coll Physicians Edinb* 2009;39:257–62.

16) Kimura, M., Naito, T., Kenmotsu, H., Taira, T., Wakuda, K., Oyakawa, T., ... & Ono, A. (2015). Prognostic impact of cancer cachexia in patients with advanced non-small cell lung cancer. *Supportive Care in Cancer*, *23*(6), 1699-1708.

17) *Overview of the SEER Program*. [cited April 8th 2011]; National Cancer Institute website]. Available from: http://seer.cancer.gov/about/overview.html.

18) Potosky AL, Riley GF, Lubitz JD et al (1993) Potential for cancer related health services research using a linked Medicare-tumor registry database. Med Care 31:732–748

19) Centers for Medicare & Medicaid Services. (2012a). 2011 edition of the statistical supplement. Retrieved November 12, 2012, from http://www.cms.gov/ResearchStatistics-Data-and-Systems/Statistics-Trends-andReports/MedicareMedicaidStatSupp/2011.html

20) Simoni-Wastila, L., Keri Yang, H. W., Blanchette, C. M., Zhao, L., Qian, J., & Dalal, A. A. (2009). Hospital and emergency department utilization associated with treatment for chronic obstructive pulmonary disease in a managed-care Medicare population. *Current medical research and opinion*, *25*(11), 2729-2735.

21) Fox, K. M., Brooks, J. M., Gandra, S. R., Markus, R., & Chiou, C.-F. (2009). Estimation of Cachexia among Cancer Patients Based on Four Definitions. *Journal of Oncology, 2009*, 693458. http://doi.org/10.1155/2009/693458

22) Fox, K. M., Brooks, J. M., Gandra, S. R., Markus, R., & Chiou, C.-F. (2009). Estimation of Cachexia among Cancer Patients Based on Four Definitions. *Journal of Oncology, 2009*, 693458. http://doi.org/10.1155/2009/693458

23) Bruera E. ABC of palliative care: anorexia, cachexia, and nutrition. *British Medical Journal*. 1997;315(7117):1219–1222.

24) Baracos, Vickie E. *Pitfalls in defining and quantifying cachexia*. Journal of cachexia, sarcopenia and muscle, 2011. 2(2):p. 71-73.

25) Congleton J. The pulmonary cachexia syndrome: aspects of energy balance. *Proc Nutr Soc* 1999;58:321–328.

26) Schols AMWJ. Pulmonary cachexia. *Int J Cardiol* 2002;85:101–110.

27) Wagner, P. D. (2008). Possible mechanisms underlying the development of cachexia in COPD. *European Respiratory Journal*, *31*(3), 492-501.

28) Donohoe, C. L., Ryan, A. M., & Reynolds, J. V. (2011). Cancer cachexia: mechanisms and clinical implications. *Gastroenterology research and practice*, *2011*.

29) M. Aapro, J. Arends, F. Bozzetti, K. Fearon, S. M. Grunberg, J. Herrstedt, J. Hopkinson, N. Jacquelin-Ravel, A. Jatoi, S. Kaasa, F. Strasser; Early recognition of malnutrition and cachexia

30) Fearon K et al., Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol*2011;12:489–95.

31) Fearon K, Arends J, Baracos V (2013) Understanding the mechanisms and treatment options in cancer cachexia. Nat Rev Clin Oncol
10:90–99

Table 2a. Characteristics of NSCLC patients with and without COPD

Covariate	COPD (%)	No COPD (%)	Total (%)	p value
No of patients	22,497 (33.60)	44,466 (66.40)	66,963	
Sex				0.1463
Males	11,626 (51.68)	22,715 (51.08)	34,341 (51.28)	
Females	10,871 (48.32)	21,751 (48.92)	32,622 (48.72)	
Race				<0.0001
White	20,414 (90.74)	38,447 (86.46)	58,861 (87.90)	
Black	1510 (6.71)	3692 (8.30)	5202 (7.77)	
American Indian	65 (0.29)	126 (0.28)	191 (0.29)	
Asian	472 (2.09)	2128 (4.79)	2600 (3.88)	
Other	36 (0.16)	73 (0.16)	109 (0.16)	
Age Mean (SD)	74.73 (6.39)	75.42 (6.94)		<0.0001
Age Group (yr)				<0.0001
66-69	4887 (21.72)	9461 (21.28)	14,348 (21.43)	
70-73	4731 (21.03)	8429 (18.96)	13,160 (19.65)	
74-79	6586 (29.28)	12,389 (27.86)	18,975 (28.34)	
80+	6293 (27.97)	14,187 (31.91)	20,480 (30.58)	
Comorbidities				
Myocardial Infarction	802 (3.56)	1878 (4.22)	2680 (4.0)	<0.0001
Congestive Heart Failure	2587 (11.50)	3829 (8.61)	6416 (9.58)	<0.0001
Peripheral Vascular Disease	1393 (6.19)	2014 (4.53)	3407 (5.09)	<0.0001
Cerebrovascular Disease	1002 (4.45)	2263 (5.09)	3265 (4.88)	0.0003
Dementia	214 (0.95)	650 (1.46)	864 (1.29)	<0.0001
Asthma	468 (2.08)	1287 (2.98)	1755 (2.62)	<0.0001
Connective Tissue Disease	306 (1.36)	643 (1.45)	949 (1.42)	0.3746
Peptic Ulcer	196 (0.87)	419 (0.94)	615 (0.92)	0.3625
Mild Liver Disease	184 (0.82)	529 (1.19)	713 (1.06)	<0.0001
Diabetes Mellitus	2355 (10.47)	5207 (11.71)	7562 (11.29)	<0.0001
Diabetes with complications	187 (0.83)	366 (0.82)	553 (0.83)	<0.9127
Hemiplegia	73 (0.32)	373 (0.84)	446 (0.67)	<0.0001

Table 2a (Continued)

Renal Disease	837 (3.72)	1713 (3.85)	2550 (3.81)	0.3997
Severe Liver Disease	34 (0.15)	130 (0.29)	164 (0.24)	0.0005
AIDS	4 (0.02)	17 (0.04)	21 (0.03)	0.158
Charlson's Comorbidity Score				0.016
0 to 2	21,545 (95.77)	42,785 (96.22)	64,330 (96.07)	
3 to 5	932 (4.14)	1650 (3.71)	2582 (3.86)	
>5	20 (0.09)	31 (0.07)	51 (0.08)	
Tumor Grade				<0.0001
Well differentiated	716 (3.18)	1847 (4.15)	2563 (3.83)	
Moderately differentiated	3093 (13.75)	6122 (13.77)	9215 (13.76)	
Poorly differentiated	5007 (22.26)	9665 (21.74)	14,672 (21.91)	
Undifferentiated	1127 (5.01)	2126 (4.78)	3253 (4.86)	
Unknown	12,554 (55.80)	24,706 (55.56)	37,260 (55.64)	
Stage				<0.0001
Localised	5078 (22.63)	7401 (16.67)	12,479 (18.67)	
Regional	5251 (23.40)	9195 (20.71)	14,446 (21.61)	
Metastatic	10,398 (46.33)	24,569 (55.33)	34,967 (52.31)	
Unstaged	181 (0.80)	503 (1.13)	564 (0.84)	
Not Applicable	1589 (7.08)	2798 (6.30)	1589 (7.08)	
Stage (TNM)				<0.0001
Stage I	4835 (21.49)	7184 (16.16)	12,019 (17.95)	
Stage II	1123 (4.99)	2282 (5.13)	3405 (5.08)	
Stage IIIA	1977 (8.79)	3417 (7.68)	5394 (8.06)	
Stage IIIB	3338 (14.84)	6680 (15.02)	10,018 (14.96)	
Stage IV	8176 (36.34)	19,675 (44.25)	27,851 (41.59)	
Unknown	3048 (13.55)	5228 (11.76)	8276 (12.36)	

Table 2b: Rates of Cachexia in NSCLC patients with and without Pre-existing COPD

	COPD		
	Total	**Cachexia**	**Rate (%)**
ALL	22497	185	0.82
Stage I	4835	27	0.55
Stage II	1123	7	0.62
Stage III	5315	38	0.71
Stage IV	8176	85	1.04

	NO-COPD		
	Total	**Cachexia**	**Rate (%)**
ALL	44459	1252	2.82
Stage I	7180	96	1.33
Stage II	2282	41	1.8
Stage III	10096	303	3
Stage IV	19,673	628	3.19

CHAPTER 4: HEALTHCARE UTILIZATION AND COSTS ASSOCIATED WITH COPD AMONG NSCLC

Introduction

Lung cancer and chronic obstructive pulmonary disease (COPD) are among leading causes of morbidity and mortality worldwide. According to the Global Burden of Disease Study 2013, lung cancer and COPD are among leading causes of years of life lost globally, especially in developed and high-income countries. (1) Lung cancer accounts for 27% of all cancer deaths with more deaths from lung cancer than from colon, prostate and breast cancer together. (2, 3) It is estimated that by 2030 it will continue to be the leading cause of cancer death due to diagnosis made at an advanced stage. (4) About 2 out of 3 people diagnosed with lung cancer are 65 or older, while less than 2% are younger than 45. Five-year survival rates are low compared to other common cancers at 16.3 percent. About 80% of lung cancers are non-small cell lung cancers (NSCLC). (1) COPD is the third leading cause of death in the US after cancer and heart disease. In 2010, COPD accounted for 134,676 deaths in the US. (5) In 2011, an estimated 12.7 million adults had been diagnosed with COPD. (6) This number could be even higher due to the fact that COPD is often an underdiagnosed disease. (7)

Lung cancer and COPD are a major public health problem due to its high incidence and related morbidity and mortality and pose significant health and economic burdens on society. According to the National Institutes of Health, the total direct medical cost of cancer in the United States was $124.6 billion in 2010. It is estimated that

approximately $12.6 billion are spent in the country on lung cancer treatment alone. Lost productivity due to early death from cancer lead to an additional $134.8 billion in 2005, of which $36.1 billion was caused by lung cancer. (8)

Previous estimates of COPD related medical costs in the US have indicated high costs incurred by patients with $37.2 billion in 2004 and $42.6 billion in 2007. (9) According to the National Heart Lung and Blood Institute, the national projected annual cost for COPD in 2010 was $49.9 billion. This includes $29.5 billion in direct health care expenditures, $8.0 billion in indirect morbidity costs and $12.4 billion in indirect mortality costs. (10) A study conducted by Ford et al in 2010 estimated total national medical costs attributable to COPD at $32.1 billion dollars annually. Absenteeism costs were $3.9 billion accounting for a total burden of $36 billion in COPD-attributable costs. Moreover, 18% of the medical costs were paid for by private insurance, 51% by Medicare, and 25% by Medicaid. The study also projected a rise in medical costs from $32.1 billion in 2010 to $49 billion by 2020. (11)

As the median age of diagnosis of lung cancer patients is high (71 years), the cost is largely incurred by the US Medicare system. Despite this burden and its expected future trend, limited data exists comparing health care resource use and costs in elderly patients with NSCLC and COPD. Most existing cost studies focus on NSCLC alone (12, 13, 14) or on all lung cancers combined. (15, 16, 17) Existing cost studies have primarily focused on estimations of chemotherapy use and costs (18, 19, 20) with little information presented regarding broader health resource utilization and costs for other service categories.

To address these information needs, the current study will employ retrospective analysis of linked Surveillance, Epidemiology and End Results (SEER)-Medicare database to examine healthcare utilization and costs in elderly NSCLC patients with and without pre-existing COPD

Methods

Data source

The SEER-Medicare database consists of the linkage of two large population-based sources of data that provide detailed information about Medicare beneficiaries with cancer. The SEER program collects information on incident cases of cancer including patient demographics, date of diagnosis, and data about the cancer (eg, histiology, stage, and grade). The SEER program covers approximately 28% of the US population. (21) Medicare is the primary health insurer for 97% of the US population 65 years and older. Medicare claims data account for all services provided by Medicare from a person's program eligibility to their death. The claims data are divided into multiple files of which three were used for data acquisition. The Medicare Provider Analysis and Review (MEDPAR) file includes all Part A short stay, long stay and skilled nursing facility bills. The Carrier Claims (or National Claims History (NCH)) file includes all Part B non-institutional provider claims (e.g. physicians, nurse practitioners ambulance providers, etc.). The Outpatient file includes claims from institutional outpatient providers (e.g. hospital outpatient departments, rural health clinics, etc.). (22)

The linkage of the SEER data with the Medicare data entails matching incident cancer cases reported in the SEER data with a master file of Medicare enrollment. (23)

The linkage of these two data sources results in a unique population-based source of information that can be used for an array of epidemiological and health services research. One of the advantages of using this data over commercial claims databases is that this data contains complete claims histories of its population (≥65 years), as compared to incomplete medical histories of those ≥65 year old patients in a commercial database that are not enrolled in a Medicare risk plan. (23)

Study population

Patients were eligible for inclusion in the study if diagnosed with first primary lung cancer between January 1, 2005 and December 31, 2010, at least 66 years of age, and continuously enrolled in Medicare Parts A and B in the 12 months prior to diagnosis. Patients were excluded if their date of death was recorded prior to or the same month as diagnosis, if they were diagnosed by autopsy, death certificate, or in an unknown month, and if they were enrolled in a health maintenance organization (HMO) at any time during the 12 months prior to diagnosis (because complete claims data were unavailable for these patients).

NSCLC diagnosis was based on the International Classification of Disease for Oncology (3rd edition, ICD-O-3) histology codes in the SEER data. Tumor stage was classified according to the sixth edition of the American Joint Commission on Cancer manual for patients diagnosed between 2005 and 2010. The diagnosis of pre-existing chronic obstructive pulmonary disease (COPD) in lung cancer patients were identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes (491 [chronic bronchitis], 492 [emphysema], 496 [chronic airway obstruction, not elsewhere classified]) before cancer diagnosis date through the Medicare

claim files. These codes were chosen based on support from previous literature as successful identifiers of COPD. (24)

A Charlson Comorbidity Index (CCI) score was calculated from the Medicare claim files to obtain a measure of patients' overall comorbidity burden. The CCI included 15 non-cancer categories of comorbidities, as defined by ICD-9-CM diagnosis codes, with associated weights corresponding to the severity of the condition of interest. (25) Because the objective of the CCI score was to evaluate underlying comorbidity burden independent of cancer, ICD-9-CM diagnosis codes for cancer were excluded from the CCI calculation for this study.

Statistical analysis

Descriptive statistics (i.e. counts, frequencies, averages) were used to summarize demographic and clinical characteristics by pre-existing COPD status (COPD vs. Non COPD). Differences between groups were assessed using Chi-square test for categorical and t-tests for continuous variables. We assessed healthcare utilization and costs for COPD and Non-COPD group stratified by stage of NSCLC. Resource utilization and costs were examined by the major service sector in which they occurred and represent the claims for services incurred within the associated service location (i.e., inpatient, skilled nursing facility, emergency department, outpatient hospital, and office visits). Person-month analyses were used for reporting healthcare utilization and costs.

Person-months were summed across the study period (60 months) and for all patients who were alive and diagnosed with NSCLC and used as the denominator. The numerator was the total utilization of a service in the same period. The result of the numerator to denominator ratio was the utilization of a service per 100 person-months

(PM). Costs were calculated as cost of a service per person-month as well as cumulative cost of all services per person-month by stage of NSCLC. Cost data represented the actual paid (i.e., reimbursed by Medicare) amounts for health services. The adjusted analyses were performed controlling for demographic (age, sex, race) and clinical (tumor grade and comorbidity score) factors using a negative binomial model for count of healthcare events and a generalized linear, gamma distribution, log-linked model for costs. T-tests were used to determine differences between groups.

Statistical significance was set at $P <= 0.05$. SAS 9.4 (SAS Institute Inc, Cary, North Carolina) was used for all data analyses. The conduct of this study was approved by National Cancer Institute and the Institutional Review Board at the University of North Carolina at Charlotte.

Results

We identified 66,963 lung cancer patients. Of these, 22,497 (33.60%) had COPD before lung cancer diagnosis. Patients differed statistically ($P<0.001$) across all demographic characteristics between pre-existing COPD and Non-COPD lung cancer patients (Table 1). The mean age of pre-existing COPD patients (75 years) was similar to Non-COPD patients. Majority of patients in the COPD (51.68%) and Non-COPD (51.08%) group were males. Caucasians accounted for the greatest proportion of lung cancer patients in both groups (90.74% and 86.46% respectively) followed by African-Americans (6.71% and 8.30%). The most common comorbid conditions among COPD and Non-COPD groups were congestive heart failure (11.50% and 8.61%), diabetes mellitus (10.47% and 11.71%), peripheral vascular disease (6.19% and 4.53%) and

cerebrovascular disease (4.45% and 5.09%). The comorbidity status of both groups, measured by the Charlson's Comorbidity Index (CCI), was statistically significant. Approximately 96% of patients accounted for CCI score less than 3 in COPD and Non-COPD groups.

Nearly all COPD and Non-COPD patients (approximately 99%) had invasive tumors. Approximately 22% of COPD patients had poorly differentiated tumor grade compared with 21% of patients in the Non-COPD group. Among COPD patients, 36.34% had stage IV lung cancer compared with 44.25% in the Non-COPD group.

Patients with pre-existing COPD had significantly higher healthcare utilization and subsequent costs across all stages of NSCLC. After adjusting for covariates, utilization and costs rose appreciably in the COPD group (Table 3). Among hospitalizations, inpatient admissions in the COPD group increased for each stage of NSCLC compared to the Non-COPD group (Stage I: 14.67 admissions per 100 PM vs 9.49 admissions per 100 PM, $P<0.0001$; Stage II: 14.13 admissions per 100 PM vs 10.78 admissions per 100 PM, $P<0.0001$; Stage III: 28.31 admissions per 100 PM vs 18.91 admissions per 100 PM, $P<0.0001$; Stage IV: 49.5 admissions per 100 PM vs 31.24 per 100 PM, $P<0.0001$). Among physician office visits, the utilization per 100 person-months increased more than 3 times in the COPD group among stages III and IV NSCLC. Overall, there were marked differences between the COPD and Non-COPD groups with higher utilization among COPD patients (Stage I: 927.36 visits per 100 PM vs 230.75 visits per 100 PM, $P<0.0001$; Stage II: 988.95 visits per 100 PM vs 241.05 visits per 100 PM, $P<0.0001$; Stage III: 1453.49 visits per 100 PM vs 387.28 visits per 100 PM, $P<0.0001$; Stage IV: 2311.94 visits per 100 PM vs 681.84 visits per 100 PM, $P<0.0001$).

A similar trend was observed for outpatient visits with an increase in utilization among COPD group (Stage I: 1136.04 visits per 100 PM vs 796 visits per 100 PM, P<0.0001; Stage II: 1325.12 visits per 100 PM vs 983.26 visits per 100 PM, P<0.0001; Stage III: 2025.47 visits per 100 PM vs 1656.64 visits per 100 PM, P<0.0001; Stage IV: 2825.73 visits per 100 PM vs 2422.26 visits per 100 PM, P<0.0001). For stage I and II NSCLC, the use of ER services were almost 2 times higher in the COPD group in contrast with the Non-COPD group (Stage I: 20.41 visits per 100 PM vs 9.78 visits per 100 PM, P<0.0001; Stage II: 24.25 visits per 100 PM vs 13.59 visits per 100 PM, P<0.0001; Stage III: 56.58 visits per 100 PM vs 33.26 visits per 100 PM, P<0.0001).

Total direct costs in patients with pre-existing COPD were significantly higher than the Non-COPD group across all services ($54,799.16 per person-month vs $41,862.91 per person-month). The subsequent hospitalization costs across all stages were also significantly higher in the COPD group compared to the Non-COPD group ($8629.77 per person-month vs $5879 per person-month, P<0.0001). Among COPD patients, the proportion of costs attributed to physician office visits were highest among stages III and IV NSCLC as reflected by healthcare utilization compared to their Non-COPD counterparts (Stage I: $468.39 per PM vs $105.90 per PM, P<0.0001; Stage II: $517.40 per PM vs $120.42 per PM, P<0.0001; Stage III: $762.63 per PM vs $195.68 per PM, P<0.0001; Stage IV: $ 1169.49 per PM vs $336.39 per PM, P<0.0001)

Outpatient visits represented the largest cost category across all services in both groups, with higher costs among the COPD group ($41,203 per person-month and $31,140.08 per person-month). The healthcare costs attributable to ER visits differed by stage of NSCLC with higher costs among COPD group in contrast with the Non-COPD

(Stage I: $71.69 per PM vs $36.66 per PM, P<0.0001; Stage II: $77.70 per PM vs $45.55 per PM, P<0.0001; Stage III: $116.48 per PM vs $76.20 per PM, P<0.0001; Stage IV: $199.71 per PM vs $131.03 per PM, P<0.0001).

Discussion

This study reported healthcare utilization and costs by COPD status for each stage of NSCLC in a large population-based sample of lung cancer patients in the United States. Overall, healthcare utilization and costs showed a consistent stage gradient; patients with a higher stage of NSCLC had higher healthcare utilization and costs in the COPD and Non-COPD groups even after adjustment. Based on COPD status, there was a significant trend towards higher utilization and costs among patients with pre-existing COPD.

Studies have indicated a number of potential factors for higher inpatient admissions among COPD patients. Chronic mucus hypersecretion, use of anticholinergics, older age, poor health related quality of life, and comorbidities were associated with hospitalizations. (26, 27, 28) Four studies showed that lower FEV1 was associated with higher risk of COPD related admissions. (27, 29, 30, 31) Miravitlles et al suggested that FEV1 impairment may explain part of the risk of frequent exacerbations and hospital admissions. (26) Several studies highlighted the association between older age and shorter time to first readmission and increased risk of hospitalization. (28, 32, 33) This may be related to the higher degree of disability and comorbidity in the older population. Patients who habitually fail to seek therapy for their exacerbations have worse health-related quality of life and are more likely to be hospitalized for the

management of an exacerbation. (34) Lau et al found that comorbid conditions such as coronary artery disease, left ventricular failure, and diabetes mellitus were significant risk factors for hospital admissions. (28)

Our study found that ER visits were 2 times higher among COPD patients in early stages of NSCLC. Previous studies have found that dyspnea, neutropenic fever, respiratory tract infections, and chronic lung disease were most common causes of ER visits among stages I/II NSCLC patients. (36, 37) Due to the increasing use of chemotherapy regimens in the outpatient setting, emergency physicians have frequently encountered complications secondary to treatment-induced febrile neutropenia. (37) Kumbhare et al reported that extremes of BMI among COPD patients were associated with higher ED visits. (38) COPD patients exhibit significant weight loss due to increased energy requirements associated with labored breathing. (39) Low BMI is shown to be associated with emergency care needs. (40, 41)

Our findings of higher costs and utilization of physician and outpatient services among the COPD group is consistent with published literature. According to Verbrugge et al, COPD is a major cause of chronic disability and a leading reason for visits to office-based physicians. (42) Douglas et al showed that COPD patients had significantly higher utilization in outpatient and physician services including outpatient surgery in office or hospital, radiology, and laboratory use. A large difference in utilization was seen in respiratory care services with 27.9% of COPD patients using pulmonary services compared with 2.4% of Non-COPD patients. Moreover, the average number of primary care visits for COPD patients was 54% higher than the Non-COPD group. (43)

We observed a general trend of increasing costs across COPD and Non-COPD groups with an increase in stage of NSCLC. In contrast, Cipriano et al found that patients diagnosed with stages I/II NSCLC followed a pattern of higher costs in the 6 month period after diagnosis followed by lower costs in the subsequent post diagnosis period. (44) This may be explained by the differences in the definitions of phases of care over which cost of cancer was calculated by Cipriano et al. versus costs of cancer care stratified by stage of cancer diagnosis in the current study. Relative costs among patients with advanced stage disease at cancer diagnosis were significantly higher than for localized stage in our study and is consistent with the trends of increasing use of aggressive care near the end of life in lung cancer.

Healthcare costs in all service areas were significantly higher in the COPD group as reflected by healthcare utilization. In our study, outpatient costs for COPD patients were highest across all service categories compared to Non-COPD patients. These results were similar to the findings reported by Douglas et al in which costs for outpatient services for COPD patients were significantly higher than inpatient costs. (43)

Our study had several important strengths. The population-based data used in the analysis included large numbers of NSCLC patients with Medicare coverage. We were able to evaluate the trajectory of care that NSCLC patients received across multiple care settings. The comprehensiveness of these data provided a detailed picture of resource use and costs across all stages of NSCLC. By using person-month estimates, we limited the analysis to only those patients who were “at risk” of receiving that type of care. This approach resulted in a more accurate estimate of service use than if we had included all patients.

Our study also had several limitations. We used administrative data to capture patients' treatment. Administrative data do not include information about non-covered services or patients' treatment choices. Pharmaceuticals (over the counter or prescription) were not included in our estimates as the study period for our study had incomplete claims for Medicare Part D. Other limitations of the analysis include those common to analyses of SEER-Medicare data (45), such as omission of patients less than 65 years old, patients enrolled in HMOs, and an inability to identify individuals, such as veterans, for whom Medicare may have incomplete claims data.

Conclusions

The current study characterized health resource utilization patterns and costs in NSCLC patients with and without pre-existing COPD. Healthcare utilization and costs among lung cancer patients with pre-existing COPD was approximately two to three times higher than the Non-COPD group. Patients with pre-existing COPD imposed a substantial direct cost burden on Medicare. The results of this study may be helpful in identifying cost-drivers and evaluate changes in practice patterns for cost containment within lung cancer landscape.

References

1) GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;385:117-71. 10.1016/S0140-6736(14)61682-2

2) Spiro SG, Silvestri GA.. One hundred years of lung cancer. Am J Respir Crit Care Med. 2005;172:523-9. 10.1164/rccm.200504-531OE

3) Shlomi D, Ben-Avi R, Balmor GR, et al. Screening for lung cancer: time for large-scale screening by chest computed tomography. Eur Respir J 2014;44:217-38. 10.1183/09031936.00164513

4) Mathers CD, Loncar D.. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006;3:e442. 10.1371/journal.pmed.0030442

5) Trends in COPD Morbidity and Mortality (2013). American Lung Association. Retrieved from http://www.lung.org/assets/documents/research/copd-trend-report.pdf

6) Centers for Disease Control and Prevention. National Center for Health Statistics: National Health Interview Survey Raw Data, 1997-2011. Analysis performed by American Lung Association Research and Health Education using SPSS and SUDAAN software.

7) Lamprecht B, Soriano JB, Studnicka M, et al. Determinants of underdiagnosis of COPD in national and international surveys. Chest 2015;148:971-85. 10.1378/chest.14-2535

8) Cancer Trends Progress Report—2011/2012 Update. Costs of Cancer Care. US National Institutes of Health. National Cancer Institute.

9) Morbidity & mortality: 2007 chartbook on cardiovascular, lung, and blood diseases. National Institutes of Health, National Heart, Lung, and Blood Institute

10) Morbidity & mortality: 2009 chartbook on cardiovascular, lung, and blood diseases. National Institutes of Health, National Heart, Lung, and Blood Institute

11) Ford, E. S., Murphy, L. B., Khavjou, O., Giles, W. H., Holt, J. B., & Croft, J. B. (2015). Total and state-specific medical and absenteeism costs of COPD among adults

aged≥ 18 years in the United States for 2010 and projections through 2020. *Chest Journal*, *147*(1), 31-45.

12) Carlson JJ, Reyes C, Oestreicher N, Lubeck D, Ramsey SD, Veenstra DL. Comparative clinical and economic outcomes of treatments for refractory non-small cell lung cancer (mNSCLC) Lung Cancer.2008;61:405–415.

13) Hoverman JR, Robertson SM. Lung cancer: a cost and outcome study based on physician practice patterns. Dis Manag. 2004;7:112–123.

14) Lang K, Marciniak MD, Faries D, Stokes M, Buesching D, Earle C, Treat J, Babineaux S, Morissette N, Thompson D. Costs of first-line doublet chemotherapy and lifetime medical care in advanced non-small-cell lung cancer in the United States. Value Health. 2009;12:481–488.

15) Chang S, Long SR, Kutikova L, Bowman L, Finley D, Crown WH, Bennett CL. Estimating the cost of cancer: results on the basis of claims data analyses for cancer patients diagnosed with seven types of cancer during 1999–2000. J Clin Oncol. 2004;22:3524–3530.

16) Kutikova L, Bowman L, Chang S, Long SR, Obasaju C, Crown WH. The economic burden of lung cancer and the associated costs of treatment failure in the United States. Lung Cancer. 2005;50:143–154.

17) Ramsey SD, Martins RG, Blough DK, Tock LS, Lubeck D, Reyes CM. Second-line and third-line chemotherapy for lung cancer: use and cost. Am J Manag Care. 2008;14:297–306.

18) Duh MS, Reynolds Weiner J, Lefebvre P, Neary M, Skarin AT. Costs associated with intravenous chemotherapy administration in patients with small cell lung cancer: a retrospective claims database analysis.Curr Med Res Opin. 2008;24:967–974. doi: 10.1185/030079908X280464.

19) Stokes ME, Muehlenbein CE, Marciniak MD, Faries DE, Motabar S, Gillespie TW, Lipscomb J, Knopf KB, Buesching DP. Neutropenia-related costs in patients treated with first-line chemotherapy for advanced non-small cell lung cancer. J Manag Care Pharm. 2009;15:669–682.

20) Ramsey SD, Howlader N, Etzioni RD, Donato B. Chemotherapy use, outcomes, and costs for older persons with advanced non-small-cell lung cancer: evidence from

surveillance, epidemiology and end results-Medicare. J Clin Oncol. 2004;22:4971–4978. doi: 10.1200/JCO.2004.05.031.

21) Overview of the SEER Program. [cited April 8th 2011]; National Cancer Institute website]. Available from: http://seer.cancer.gov/about/overview.html.

22) Centers for Medicare & Medicaid Services. (2012a). 2011 edition of the statistical supplement. Retrieved November 12, 2012, from http://www.cms.gov/ResearchStatistics-Data-and-Systems/Statistics-Trends-andReports/MedicareMedicaidStatSupp/2011.html

23) Potosky AL, Riley GF, Lubitz JD et al (1993) Potential for cancer related health services research using a linked Medicare-tumor registry database. Med Care 31:732–748

24) Simoni-Wastila, L., Keri Yang, H. W., Blanchette, C. M., Zhao, L., Qian, J., & Dalal, A. A. (2009). Hospital and emergency department utilization associated with treatment for chronic obstructive pulmonary disease in a managed-care Medicare population. *Current medical research and opinion*, *25*(11), 2729-2735.

25) Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemio l. 1992;45:613-9

26) Miravitlles M, Guerrero T, Mayordomo C, Sanchez-Agudo L, Nicolau F, Segu JL. Factors associated with increased risk of exacerbation and hospital admission in a cohort of ambulatory COPD patients: a multiple logistic regression analysis. The EOLO Study Group. Respiration. 2000;67:495–501.

27) Garcia-Aymerich J, Farrero E, Felez MA, Izquierdo J, Marrades RM, Anto JM. Risk factors of readmission to hospital for a COPD exacerbation: a prospective study. Thorax. 2003;58:100–5.

28) Lau AC, Yam LY, Poon E. Hospital re-admission in patients with acute exacerbation of chronic obstructive pulmonary disease. Respiratory Medicine. 2001;95:876–84.

29) Garcia-Aymerich J, Monso E, Marrades RM, Escarrabill J, Felez MA, Sunyer J, Anto JM. Risk factors for hospitalization for a chronic obstructive pulmonary disease exacerbation. EFRAM study. American Journal of Respiratory & Critical Care Medicine. 2001;164:1002–7.

30) Gudmundsson G, Gislason T, Janson C, Lindberg E, Hallin R, Ulrik CS, Brøndum E, Nieminen MM, Aine T, Bakke P. Risk factors for rehospitalisation in COPD: role of health status, anxiety and depression. Eur Respir J. 2005;26:414–19.

31) Cao Z, Ong KC, Eng P, Tan WC, Ng TP. Frequent hospital readmissions for acute exacerbation of COPD and their associated factors. Respirology. 2006;11:188–95.

32) Soler-Cataluña JJ, Martínez-García MÁ, Román Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax. 2005;60:925–31.

33) Gadoury MA, Schwartzman K, Rouleau M, Maltais F, Julien M, Beaupré A, Renzi P, Bégin R, Nault D, Bourbeau J. Self-management reduces both short-and long-term hospitalisation in COPD. Eur Respir J. 2005;26:853–7.

34) Bahadori, K., & FitzGerald, J. M. (2007). Risk factors of hospitalization and readmission of patients with COPD exacerbation–systematic. *International Journal of COPD*, *2*(3), 241-251.

35) Mayer DK, Travers D, Wyss A, Leak A, Waller A. Why do patients with cancer visit emergency departments? Results of a 2008 population study in North Carolina. J Clin Oncol. 2011;29:2683–2688.

36) Kotajima, F., Kobayashi, K., Sakaguchi, H., & Nemoto, M. (2014). Lung cancer patients frequently visit the emergency room for cancer-related and-unrelated issues. *Molecular and clinical oncology*, *2*(2), 322-326.

37) Sadik, M., Ozlem, K., Huseyin, M., AliAyberk, B., Ahmet, S., & Ozgur, O. (2014). Attributes of cancer patients admitted to the emergency department in one year. *World journal of emergency medicine*, *5*(2), 85.

38) Kumbhare, S. D., Beiko, T., Wilcox, S. R., & Strange, C. Characteristics of COPD Patients Using United States Emergency Care or Hospitalization. *Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation*, *3*(2), 539-548.

39) Wouters EFM. Nutrition and metabolism in COPD. ***Chest***. 2000;117(5 Suppl 1):274S-280S.

40) Hallin R, Gudmundsson G, Ulrik CS, et al. Nutritional status and long-term mortality in hospitalised patients with chronic obstructive pulmonary disease (COPD). *Respir Med*. 2007. 101(9):1954-1960.

41) Liu Y, et al. Body mass index, respiratory conditions, asthma, and chronic obstructive pulmonary disease. *Respir Med*. 109(7): p. 851-859.

42) Verbrugge LMPatrick DL Seven chronic conditions: their impact on US adults' activity levels and use of medical services. *Am J Public Health.*1995;85173- 182

43) Mapel, D. W., Hurley, J. S., Frost, F. J., Petersen, H. V., Picchi, M. A., & Coultas, D. B. (2000). Health care utilization in chronic obstructive pulmonary disease: a case-control study in a health maintenance organization. *Archives of Internal Medicine*, *160*(17), 2653-2658.

44) Cipriano, L. E., Romanus, D., Earle, C. C., Neville, B. A., Halpern, E. F., Gazelle, G. S., & McMahon, P. M. (2011). Lung cancer treatment costs, including patient responsibility, by disease stage and treatment modality, 1992 to 2003. *Value in Health*, *14*(1), 41-52.

45) Warren JL, Klabunde CN, Schrag D, et al. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. Medical Care. 2002; 40:IV-3–IV-18

Table 3a. Characteristics of NSCLC patients with and without COPD

Covariate	**COPD (%)**	**No COPD (%)**	**Total (%)**	**p value**
No of patients	22,497 (33.60)	44,466 (66.40)	66,963	
Sex				0.1463
Males	11,626 (51.68)	22,715 (51.08)	34,341 (51.28)	
Females	10,871 (48.32)	21,751 (48.92)	32,622 (48.72)	
Race				<0.0001
White	20,414 (90.74)	38,447 (86.46)	58,861 (87.90)	
Black	1510 (6.71)	3692 (8.30)	5202 (7.77)	
American Indian	65 (0.29)	126 (0.28)	191 (0.29)	
Asian	472 (2.09)	2128 (4.79)	2600 (3.88)	
Other	36 (0.16)	73 (0.16)	109 (0.16)	
Age Mean (SD)	74.73 (6.39)	75.42 (6.94)		<0.0001
Age Group (yr)				<0.0001
66-69	4887 (21.72)	9461 (21.28)	14,348 (21.43)	
70-73	4731 (21.03)	8429 (18.96)	13,160 (19.65)	
74-79	6586 (29.28)	12,389 (27.86)	18,975 (28.34)	
80+	6293 (27.97)	14,187 (31.91)	20,480 (30.58)	
Comorbidities				
Myocardial Infarction	802 (3.56)	1878 (4.22)	2680 (4.0)	<0.0001
Congestive Heart Failure	2587 (11.50)	3829 (8.61)	6416 (9.58)	<0.0001
Peripheral Vascular Disease	1393 (6.19)	2014 (4.53)	3407 (5.09)	<0.0001
Cerebrovascular Disease	1002 (4.45)	2263 (5.09)	3265 (4.88)	0.0003

Table 3a (Continued)

Dementia	214 (0.95)	650 (1.46)	864 (1.29)	<0.0001
Asthma	468 (2.08)	1287 (2.98)	1755 (2.62)	<0.0001
Connective Tissue Disease	306 (1.36)	643 (1.45)	949 (1.42)	0.3746
Peptic Ulcer	196 (0.87)	419 (0.94)	615 (0.92)	0.3625
Mild Liver Disease	184 (0.82)	529 (1.19)	713 (1.06)	<0.0001
Diabetes Mellitus	2355 (10.47)	5207 (11.71)	7562 (11.29)	<0.0001
Diabetes with complications	187 (0.83)	366 (0.82)	553 (0.83)	<0.9127
Hemiplegia	73 (0.32)	373 (0.84)	446 (0.67)	<0.0001
Renal Disease	837 (3.72)	1713 (3.85)	2550 (3.81)	0.3997
Severe Liver Disease	34 (0.15)	130 (0.29)	164 (0.24)	0.0005
AIDS	4 (0.02)	17 (0.04)	21 (0.03)	0.158
Charlson's Comorbidity Score				0.016
0 to 2	21,545 (95.77)	42,785 (96.22)	64,330 (96.07)	
3 to 5	932 (4.14)	1650 (3.71)	2582 (3.86)	
>5	20 (0.09)	31 (0.07)	51 (0.08)	
Tumor Grade				<0.0001
Well differentiated	716 (3.18)	1847 (4.15)	2563 (3.83)	
Moderately differentiated	3093 (13.75)	6122 (13.77)	9215 (13.76)	
Poorly differentiated	5007 (22.26)	9665 (21.74)	14,672 (21.91)	
Undifferentiated	1127 (5.01)	2126 (4.78)	3253 (4.86)	
Unknown	12,554 (55.80)	24,706 (55.56)	37,260 (55.64)	
Stage				<0.0001
Localised	5078 (22.63)	7401 (16.67)	12,479 (18.67)	
Regional	5251 (23.40)	9195 (20.71)	14,446 (21.61)	
Metastatic	10,398 (46.33)	24,569 (55.33)	34,967 (52.31)	
Unstaged	181 (0.80)	503 (1.13)	564 (0.84)	
Not Applicable	1589 (7.08)	2798 (6.30)	1589 (7.08)	

Table 3a (Continued)

Stage (TNM)				<0.0001
Stage I	4835 (21.49)	7184 (16.16)	12,019 (17.95)	
Stage II	1123 (4.99)	2282 (5.13)	3405 (5.08)	
Stage IIIA	1977 (8.79)	3417 (7.68)	5394 (8.06)	
Stage IIIB	3338 (14.84)	6680 (15.02)	10,018 (14.96)	
Stage IV	8176 (36.34)	19,675 (44.25)	27,851 (41.59)	
Unknown	3048 (13.55)	5228 (11.76)	8276 (12.36)	

Table 3b Unadjusted Healthcare Utilization and Costs among NSCLC patients with and without Pre-existing COPD

Service	COPD-status	Lung Cancer Stage	Person-Months	Utilization per 100 Person-Months	Cost per Person-Month	Utilization Difference per 100 Person-Months	Cost Difference
Admissions	Non-COPD	I	196,188	7.71	$988.82		
Admissions	Non-COPD	II	52,978	8.69	$1,071.27		
Admissions	Non-COPD	III	122,982	15.19	$1,697.22		
Admissions	Non-COPD	IV	132,628	25	$2,607.27		
Admissions	COPD	I	111,039	11.73	$1,229.49	4.02*	$240.68*
Admissions	COPD	II	22,298	11.29	$1,174.14	2.6*	$102.87*
Admissions	COPD	III	58,810	22.44	$2,205.70	7.25*	$508.48*
Admissions	COPD	IV	50,791	39.23	$3,820.70	14.23*	$1213.42*
SNF	NON-COPD	I	196,188	1.01	$83.15		
SNF	NON-COPD	II	52,978	0.98	$74.79		
SNF	NON-COPD	III	122,982	2.1	$167.82		
SNF	NON-COPD	IV	132,628	3.85	$284.29		
SNF	COPD	I	111,039	2.19	$171.96	1.18*	$88.8*
SNF	COPD	II	22,298	2.05	$161.22	1.07	$86.43
SNF	COPD	III	58,810	4.17	$308.41	2.07	$140.60
SNF	COPD	IV	50,791	7.43	$540.15	3.58*	$255.87*
Physician-Visits	Non-COPD	I	196,188	168.76	$106.57		
Physician-Visits	Non-COPD	II	52,978	189.87	$129.51		
Physician-Visits	Non-COPD	III	122,982	314.46	$201.39		
Physician-Visits	Non-COPD	IV	132,628	541.56	$338.56		

Table 3b (Continued)

Physician-Visits	COPD	I	111,039	745.27	$463.86	576.51*	$357.3*
Physician-Visits	COPD	II	22,298	818.16	$528.64	628.29*	$399.13*
Physician-Visits	COPD	III	58,810	1222.79	$764.80	908.33*	$563.41*
Physician-Visits	COPD	IV	50,791	1863.74	$1,143.63	1322.18*	$805.07*
ER-Visits	NO-COPD	I	196,188	8.08	$35.19		
ER-Visits	NO-COPD	II	52,978	8.72	$36.59		
ER-Visits	NO-COPD	III	122,982	15.59	$67.07		
ER-Visits	NO-COPD	IV	132,628	25.85	$109.46		
ER-Visits	COPD	I	111,039	14.25	$61.54	6.17	$26.35
ER-Visits	COPD	II	22,298	15.71	$73.08	6.99*	$36.49*
ER-Visits	COPD	III	58,810	23.42	$105.27	7.83*	$38.2*
ER-Visits	COPD	IV	50,791	39.37	$171.96	13.52*	$62.5*
Outpatient	NO-COPD	I	196,188	506.92	$4,409.26		
Outpatient	NO-COPD	II	52,978	600.89	$6,540.81		
Outpatient	NO-COPD	III	122,982	1026.58	$11,520.51		
Outpatient	NO-COPD	IV	132,628	1469.5	$15,647.92		
Outpatient	COPD	I	111,039	658.45	$5,127.05	151.53*	$717.8*
Outpatient	COPD	II	22,298	767.86	$7,032.49	166.97*	$491.69*
Outpatient	COPD	III	58,810	1193.58	$11,141.92	167*	$-378.59*
Outpatient	COPD	IV	50,791	1668.95	$13,793.35	199.45*	$-1854.57*

*P<0.05 SNF=Skilles Nursing Facility ER=Emergency Room

Table 3c Adjusted Healthcare Utilization and Costs among NSCLC patients with and without Pre-existing COPD

Service	COPD-status	Lung Cancer Stage	Person-Months	Utilization per 100 Person-Months	Cost per Person-Month	Utilization Difference per 100 Person-Months	Cost Difference
Admissions	Non-COPD	I	196,188	9.49	836.61		
Admissions	Non-COPD	II	52,978	10.78	946.31		
Admissions	Non-COPD	III	122,982	18.91	1558.66		
Admissions	Non-COPD	IV	132,628	31.24	2537.42		
Admissions	COPD	I	111,039	14.67	1235.86	5.18*	$399.35*
Admissions	COPD	II	22,298	14.13	1193.67	3.35*	$247.37*
Admissions	COPD	III	58,810	28.31	2274.88	9.4*	$716.22*
Admissions	COPD	IV	50,791	49.5	3925.36	18.26*	$1387.95*
SNF	NON-COPD	I	196,188	1.23	104.10		
SNF	NON-COPD	II	52,978	1.2	103.11		
SNF	NON-COPD	III	122,982	2.59	208.31		
SNF	NON-COPD	IV	132,628	4.78	380.49		
SNF	COPD	I	111,039	2.73	225.36	1.5*	$121.26*
SNF	COPD	II	22,298	2.56	214.12	1.36	$111.01
SNF	COPD	III	58,810	5.24	412.34	2.65	$204.03
SNF	COPD	IV	50,791	9.34	730.26	4.56	$349.77*
Physician-Visits	Non-COPD	I	196,188	230.75	105.90		
Physician-Visits	Non-COPD	II	52,978	241.05	120.42		
Physician-Visits	Non-COPD	III	122,982	387.28	195.68		
Physician-Visits	Non-COPD	IV	132,628	681.84	336.39		

Table 3c (Continued)

Physician-Visits	COPD	I	111,039	927.36	468.39	696.61*	$362.49*
Physician-Visits	COPD	II	22,298	988.95	517.40	747.9*	$396.97*
Physician-Visits	COPD	III	58,810	1453.49	762.63	1066.21*	$566.95*
Physician-Visits	COPD	IV	50,791	2311.94	1169.49	1630.1*	$833.09*
ER-Visits	NO-COPD	I	196,188	9.78	36.66		
ER-Visits	NO-COPD	II	52,978	13.59	45.55		
ER-Visits	NO-COPD	III	122,982	19.73	76.20		
ER-Visits	NO-COPD	IV	132,628	33.26	131.03		
ER-Visits	COPD	I	111,039	20.41	71.69	10.63*	$35.04*
ER-Visits	COPD	II	22,298	24.25	77.70	10.66*	$32.15*
ER-Visits	COPD	III	58,810	31.85	116.48	12.12*	$40.28*
ER-Visits	COPD	IV	50,791	56.58	199.71	23.32*	$68.68*
Outpatient	NO-COPD	I	196,188	796	4660.00		
Outpatient	NO-COPD	II	52,978	983.26	5745.64		
Outpatient	NO-COPD	III	122,982	1656.64	9708.94		
Outpatient	NO-COPD	IV	132,628	2422.26	14025.50		
Outpatient	COPD	I	111,039	1136.04	6202.37	340.04*	$1524.36*
Outpatient	COPD	II	22,298	1325.12	7486.42	341.86*	$1740.78*
Outpatient	COPD	III	58,810	2025.47	11493.13	368.83*	$1784.19*
Outpatient	COPD	IV	50,791	2825.73	16021.90	403.47*	$1996.39*

*P<0.05 SNF=Skilled Nursing Facility
ER=Emergency Room

CHAPTER 5: CONCLUSIONS

Conclusion

This retrospective analyses conducted within the SEER-Medicare linked dataset in the NSCLC populations illustrated the impact of pre-existing COPD and its subtypes: chronic bronchitis and emphysema on overall survival, the importance of documenting cachexia, and the healthcare utilization and costs in this population. This work established that it is possible to assess time to death, risk of mortality, healthcare resource use and costs through the use of a population-based, nationally validated claims dataset of patients over age 65, a group that is typically underrepresented in clinical trials. The key findings of this research are: elderly NSCLC patients with pre-existing COPD had shorter survival especially in the early stages of lung cancer, with a decrease in survival from Stage I to Stage IV. Among COPD subtypes, chronic bronchitis had shorter survival at every stage of lung cancer compared to emphysema. Healthcare utilization and costs among lung cancer patients with pre-existing COPD was approximately two to three times higher than the Non-COPD group. Even though 60% to 80% of patients with cancer suffer from significant weight loss (49), the current study identified a very small proportion of patients with documented cancer cachexia. This indicated that cachexia is underestimated and under-documented by the healthcare community.

Implications

One of the most difficult challenges of screening programs for lung cancer is the appropriate selection of patients with an optimal risk-benefit ratio. While low-dose computed tomography (LDCT) is an effective procedure for the early detection of lung cancer in high-risk patients, determining which patients should be screened for the cancer in a primary care setting is difficult (50). The results of this study may indicate that screening for NSCLC in patients who have been diagnosed with COPD may have an excellent risk benefit ratio for early lung cancer detection. Moreover, COPD is frequently underdiagnosed and misdiagnosed (50). Therefore COPD screening should be initiated in lung cancer patients as early as possible as diagnosis of COPD may be very important in identifying mortality risks across all stages of lung cancer.

Given that clinical guidelines for NSCLC treatment provide clinicians with little guidance in caring for patients with pre-existing COPD, (51) results of this study have clinical implications for not only the early identification of those at greater risk of NSCLC prognosis but also those who will benefit from more optimal targeted treatment in both early and advanced stages of cancer. There is growing evidence suggesting that altered DNA methylation in association with chronic bronchitis plays a role in promoting lung carcinogenesis (52). It is plausible that several candidate risk genes and pathways identified by lung cancer studies may be shared by these two diseases and could constitute potential targets for the newly developed drugs (eg, demethylating agents and histone deacetylase–inhibiting agents) that modify epigenetic alterations.

The current study characterized health resource utilization patterns and costs in NSCLC patients with and without pre-existing COPD. Patients with pre-existing COPD

imposed a substantial direct cost burden on Medicare. The results of this study may be helpful in identifying cost-drivers and evaluate changes in practice patterns for cost containment within lung cancer landscape. COPD is considered as an ambulatory-care sensitive condition. Section 3025 of the Affordable Care Act (ACA) enacted the Hospital Readmissions Reduction Program financially penalizing hospitals for high readmission rates among specified conditions including COPD (53). It is expected that out-patient and physician visits related to COPD may continue to increase and inpatient hospitalizations may stay the same or potentially decrease. The results of this study may be helpful to evaluate the effect of changes in the practice of COPD management. Improved symptom management could reduce demand for high-cost medical resources and reduce overall COPD-related costs.

Data on resource use and costs stratified by stages of cancer among patients with lung cancer may be important in informing the overall allocation of healthcare resources, in defining potential cost savings from disease prevention, and in evaluating the cost-effectiveness of new interventions. These studies should provide information to help guide policy decisions concerning the provision and payment for cancer care

For cachexia, the results of the current study may increase knowledge and awareness of this underrepresented condition and may enable physicians to identify, diagnose, and treat all cases of cachexia. It will also aid in characterizing the burden of cancer-cachexia in terms of mortality, health-related quality of life, and healthcare resource utilization.

Recommendations

As is fitting for a dissertation project intended to begin a long-term research program, many new research questions have emerged during the conduct of this study. It is important to assess the influence of COPD disease severity and smoking history on survival among NSCLC patients with pre-existing COPD. Future research should include prospective cohort studies on COPD patients who develop lung cancer including COPD disease severity and smoking history. Further research is also required to explore the type of tumors that NSCLC patients with pre-existing COPD develop (adenocarcinoma, squamous cell carcinoma, large cell carcinoma) and the sites of metastases.

There is a great need for comparing and sharing data coming from existing and future studies of COPD and lung cancer. Cohort studies of each disease should be designed to collect data relevant to both diseases. Animal models should be developed in both diseases as these models are currently lacking. Animal models and early-phase clinical trials could offer insights on the mechanisms of the disease, identify shared genetic and epigenetic risk factors, identify and validate biomarkers for COPD development, as well as identify target population for chemo-prevention.

To build on the results of this work, data from additional sources would add value, such as electronic health records thoroughly integrated into hospital systems that provide multidisciplinary in- and outpatient oncology care. In the current study, we had demographic, clinical, and claims information for patient at the stage of diagnosis. Future studies should include large data bases which also include patient's cancer progression. Additionally, contemporary data (within last five years) should be used to assess healthcare resource use, treatment patterns, and costs. These studies will provide most

current trends within cancer-care including most recent advances in treatments such as immunotherapies. For cachexia, refinement of diagnostic criteria as well as large contemporary datasets with cachexia diagnostic criteria and clinical outcomes is necessary for further research on cachexia among lung cancer patients.

The ability to capture more extensive clinical data to complement or explain the context of the claims data utilized in this study would provide a more complete picture of the factors impacting outcomes over time as patients interact with the health care system.

REFERENCES

1) What are the key statistics about lung cancer(2013), American Cancer Society. Retrieved from http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-key-statistics

2) Lu, C., Onn, A., & Vaporciyan, A. (2010). 78: Cancer of the lung, Holland-Frei Cancer Medicine. People's Medical Publishing House.

3) Horn, L; Lovly, CM; Johnson, DH (2015). "Chapter 107: Neoplasms of the lung". In Kasper, DL; Hauser, SL; Jameson, JL; Fauci, AS; Longo, DL; Loscalzo, J. Harrison's Principles of Internal Medicine (19th ed.). McGraw-Hill.

4) Cancer Facts & Figures (2016), American Cancer Society's publication, Retrieved from http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-047079.pdf

5) Centers for Disease Control and Prevention (CDC. (2012). Chronic obstructive pulmonary disease among adults--United States, 2011. MMWR. Morbidity and mortality weekly report, 61(46), 938. Retrieved from http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6146a2.htm

6) Trends in COPD Morbidity and Mortality (2013). American Lung Association. Retrieved from http://www.lung.org/assets/documents/research/copd-trend-report.pdf

7) Centers for Disease Control and Prevention. National Center for Health Statistics: National Health Interview Survey Raw Data, 1997-2011. Analysis performed by American Lung Association Research and Health Education using SPSS and SUDAAN software.

8) Fearon K et al., Definition and classification of cancer cachexia: an international consensus. Lancet Oncol2011;12:489–95.

9) Benner A et al., Definition and classification of cancer cachexia: an international consensus. Lancet Oncol2013;10:90–9.

10) Bennani-Baiti N et al., What is cancer anorexia-cachexia syndrome? A historical perspective. J R Coll Physicians Edinb 2009;39:257–62.

11) von Haehling S et al., Cachexia as a major underestimated and unmet medical need: facts and numbers. J Cachexia Sarcopenia Muscle 2010;1:1–5.

12) Vaughan VC et al., Cancer cachexia: impact, mechanisms and emerging treatments. J Cachexia Sarcopenia Muscle 2013;4:95–109

13) Dodson S, et al., Muscle wasting in cancer cachexia: clinical implications, diagnosis, and emerging treatment strategies. Annu Rev Med 2011;62:265–79.

14) Suzuki H et al., Cancer cachexia-pathophysiology and management. J Gastroenterol 2013;48:574–594.

15) Schols AM, Soeters PB, Dingemans AM, Mostert R, Frantzen PJ, Wouters EF. Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. Am Rev Respir Dis 1993;147:1151–1156.

16) Mostert R, Goris A, Weling-Scheepers C, Wouters EF, Schols AM. Tissue depletion and health related quality of life in patients with chronic obstructive pulmonary disease. Respir Med 2000;94:859–867.

17) Engelen MP, Schols AM, Baken WC, Wesseling GJ, Wouters EF. Nutritional depletion in relation to respiratory and peripheral skeletal muscle function in out-patients with COPD. Eur Respir J 1994;7:1793–1797.

18) Vestbo J, Prescott E, Almdal T, Dahl M, Nordestgaard BG, Andersen T, et al. Body mass, fat-free body mass, and prognosis in patients with chronic obstructive pulmonary disease from a random population sample: findings from the Copenhagen City Heart Study. Am J Respir Crit Care Med 2006;173:79–83.

19) Schols AM, Broekhuizen R, Weling-Scheepers CA, Wouters EF. Body composition and mortality in chronic obstructive pulmonary disease. Am J Clin Nutr 2005;82:53–59.

20) Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE; Lung Health Study Research Group. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. Ann Intern Med. 2005; 142:233–239.

21)Young RP, Hopkins RJ, Christmas T, Black PN, Metcalf P, Gamble GD. COPD prevalence is increased in lung cancer, independent of age, sex and smoking history. Eur Respir J. 2009; 34(2):380-6.

22)Wasswa-Kintu S, Gan WQ, Man SFP, Pare PD, Sin DD. Relationship between reduced forced expiratory volume in one second and the risk of lung cancer: a systematic review and meta-analysis.Thorax. 2005;60:570–575.

23) Calabro E, Randi G, La Vecchia C, Sverzellati N, Marchiano A, Villani M et al. . Lung function predicts lung cancer risk in smokers: a tool for targeting screening programmes. Eur Respir J. 2010; 35(6):146-151.

24) Barnes PJ. New concepts in chronic obstructive pulmonary disease. Annu Rev Med. 2003; 54:113–129.

25) Houghton, A. M. (2013). Mechanistic links between COPD and lung cancer.Nature Reviews Cancer, 13(4), 233-245.

26) Kim, W. J., & Do Lee, S. (2015). Candidate genes for COPD: current evidence and research. International journal of chronic obstructive pulmonary disease, 10, 2249.

27) Greulich, T., & Vogelmeier, C. F. (2015). Alpha-1-antitrypsin deficiency: increasing awareness and improving diagnosis. Therapeutic advances in respiratory disease, 1753465815602162.

28) Carrell, R. W., & Lomas, D. A. (2002). Alpha1-antitrypsin deficiency—a model for conformational diseases. New England Journal of Medicine,346(1), 45-53.

29) Hanahan, D. & Weinberg, R. A. Hallmarks of cancer: the next generation. Cell 144, 646–674 (2011). The definitive review on the key features that define malignancy.

30) Gavrilescu, L. C., & Denkers, E. Y. (2003). Apoptosis and the balance of homeostatic and pathologic responses to protozoan infection. Infection and immunity, 71(11), 6109-6115.

31) Amos, C. I. et al. Genome-wide association scan of tag SNPs identifies a susceptibility locus for lung cancer at 15q25.1. Nature Genet. 40, 616–622 (2008).

32) Belinsky, S. A. et al. Aberrant promoter methylation in bronchial epithelium and sputum from current and former smokers. Cancer Res. 62, 2370–2377 (2002).

33) Hogg, J. C. et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. N. Engl. J. Med. 350, 2645–2653 (2004).

34) Cancer Trends Progress Report—2011/2012 Update. Costs of Cancer Care. US National Institutes of Health. National Cancer Institute.

35) Morbidity & mortality: 2007 chartbook on cardiovascular, lung, and blood diseases. National Institutes of Health, National Heart, Lung, and Blood Institute

36) Morbidity & mortality: 2009 chartbook on cardiovascular, lung, and blood diseases. National Institutes of Health, National Heart, Lung, and Blood Institute

37) Ford, E. S., Murphy, L. B., Khavjou, O., Giles, W. H., Holt, J. B., & Croft, J. B. (2015). Total and state-specific medical and absenteeism costs of COPD among adults aged≥ 18 years in the United States for 2010 and projections through 2020. Chest Journal, 147(1), 31-45.

38) R.P. Young, et al. Airflow limitation and histology-shift in the national lung screening trial: the NLST–ACRIN Cohort Substudy. Am. J. Respir. Crit. Care Med. (2015)

39) Kimura, M., Naito, T., Kenmotsu, H., Taira, T., Wakuda, K., Oyakawa, T., ... & Ono, A. (2015). Prognostic impact of cancer cachexia in patients with advanced non-small cell lung cancer. Supportive Care in Cancer, 23(6), 1699-1708.

40) Carlson JJ, Reyes C, Oestreicher N, Lubeck D, Ramsey SD, Veenstra DL. Comparative clinical and economic outcomes of treatments for refractory non-small cell lung cancer (mNSCLC) Lung Cancer.2008;61:405–415.

41) Hoverman JR, Robertson SM. Lung cancer: a cost and outcome study based on physician practice patterns. Dis Manag. 2004;7:112–123.

42) Lang K, Marciniak MD, Faries D, Stokes M, Buesching D, Earle C, Treat J, Babineaux S, Morissette N, Thompson D. Costs of first-line doublet chemotherapy and lifetime medical care in advanced non-small-cell lung cancer in the United States. Value Health. 2009;12:481–488.

43) Chang S, Long SR, Kutikova L, Bowman L, Finley D, Crown WH, Bennett CL. Estimating the cost of cancer: results on the basis of claims data analyses for cancer patients diagnosed with seven types of cancer during 1999–2000. J Clin Oncol. 2004;22:3524–3530.

44) Kutikova L, Bowman L, Chang S, Long SR, Obasaju C, Crown WH. The economic burden of lung cancer and the associated costs of treatment failure in the United States. Lung Cancer. 2005;50:143–154.

45) Ramsey SD, Martins RG, Blough DK, Tock LS, Lubeck D, Reyes CM. Second-line and third-line chemotherapy for lung cancer: use and cost. Am J Manag Care. 2008;14:297–306.

46) Duh MS, Reynolds Weiner J, Lefebvre P, Neary M, Skarin AT. Costs associated with intravenous chemotherapy administration in patients with small cell lung cancer: a retrospective claims database analysis.Curr Med Res Opin. 2008;24:967–974. doi: 10.1185/030079908X280464.

47) Stokes ME, Muehlenbein CE, Marciniak MD, Faries DE, Motabar S, Gillespie TW, Lipscomb J, Knopf KB, Buesching DP. Neutropenia-related costs in patients treated with first-line chemotherapy for advanced non-small cell lung cancer. J Manag Care Pharm. 2009;15:669–682.

48) Ramsey SD, Howlader N, Etzioni RD, Donato B. Chemotherapy use, outcomes, and costs for older persons with advanced non-small-cell lung cancer: evidence from surveillance, epidemiology and end results-Medicare. J Clin Oncol. 2004;22:4971–4978.

49) Bruera E. ABC of palliative care: anorexia, cachexia, and nutrition. British Medical Journal. 1997;315(7117):1219–1222.

50) Sekine Y, Behnia M, Fujisawa T. Impact of COPD on pulmonary complications and on long-term survival of patients undergoing surgery for NSCLC. Lung Cancer 2002; 37: 95–101.

51) Howington JA , Blum MG , Chang AC , Balekian AA , Murthy SC . Treatment of stage I and II non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013 ;143(5_suppl):e278S-e313S

52) Bruse, S., Petersen, H., Weissfeld, J., Picchi, M., Willink, R., Do, K., ... & Tesfaigzi, Y. (2014). Increased methylation of lung cancer-associated genes in sputum DNA of former smokers with chronic mucous hypersecretion. Respiratory research, 15(1), 2.

53) Readmissions Reduction Program (2016). Centers for Medicare and Medicaid Services. Retrieved from https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/Readmissions-Reduction-Program.html