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Cardiovascular comorbidities and survival of lung cancer patients: Medicare data based analysis

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ABSTRACT

Objectives: To evaluate the role of cardiovascular disease (CVD) comorbidity in survival of patients with non-small cell lung cancer (NSCLC).
Materials and methods: The impact of seven CVDs (at the time of NSCLC diagnosis and during subsequent follow-up) on overall survival was studied for NSCLC patients aged 65+ years using the Surveillance, Epidemiology, and End Results data linked to the U.S. Medicare data, cancer stage- and treatment-specific. Cox regression was applied to evaluate death hazard ratios of CVDs in univariable and multivariable analyses (controlling by age, TNM statuses, and 78 non-CVD comorbidities) and to investigate the effects of 128 different combinations of CVDs on patients' survival.
Results: Overall, 95,167 patients with stage I ($n = 29{,}836$, 31.4%), II ($n = 5133$, 5.4%), IIIA ($n = 11{,}884$, 12.5%), IIIB ($n = 18{,}020$, 18.9%), and IV ($n = 30{,}294$, 31.8%) NSCLC were selected. Most CVDs increased the risk of death for stages I–IIIB patients, but did not significantly impact survival of stage IV patients. The worse survival of patients was associated with comorbid heart failure, myocardial infarction, and cardiac arrhythmias that occurred during a period of follow-up: HRs up to 1.85 ($p < 0.001$), 1.96 ($p < 0.05$), and 1.67 ($p < 0.001$), respectively, varying by stage and treatment. The presence of hyperlipidemia at baseline (HR down to 0.71, $p < 0.05$) was associated with better prognosis. Having multiple co-existing CVDs significantly increased mortality for all treatments, especially for stages I and II patients treated with surgery (HRs up to 2.89, $p < 0.05$) and stages I–IIIB patients treated with chemotherapy (HRs up to 2.59, $p < 0.001$) and chemotherapy and radiotherapy (HRs up to 2.20, $p < 0.001$).
Conclusion: CVDs impact the survival of NSCLC patients, particularly when multiple co-existing CVDs are present; the impacts vary by stage and treatment. This data should be considered in improving cancer treatment selection process for such potentially challenging patients as the elderly NSCLC patients with CVD comorbidities.

1. Introduction

Lung cancer is a disease of older adults, as approximately 69% of new diagnoses are made in patients over 65 years old [1]. Therefore, it is not surprising that more than 70% of non-small cell lung cancer (NSCLC) patients have at least one comorbid disease [2]. Although comorbidities can affect cancer risk, detection, evolution, treatment choice, and survival [3,4], the common perception of rapid deterioration and subsequent death due to lung cancer has minimized the importance of assessing comorbidities to lung cancer outcomes [5]. Previous studies have shown that the effect of comorbidities is greatest among malignancies with more indolent disease progression and more prolonged survival (i.e., prostate cancer); however, comorbidities still may contribute to lung cancer survival, especially counting for patients' heterogeneity [6,7]. Although the clinical ramifications of comorbidities are now better appreciated [8], few studies have analyzed the specific effects of comorbidities on lung cancer survival while considering stage and treatment.

Cardiovascular diseases (CVDs) are the most frequently observed comorbidities (23% of lung cancer patients) [9], and

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they can worsen lung cancer survival by limiting cardiovascular reserves, as well as by limiting treatment selection and tolerance [8]. The precise understanding of the effects of CVDs on lung cancer survival is limited, in part because most lung cancer clinical trials exclude older patients with comorbidities to avoid obscuration of cancer treatment effects by non-lung cancer specific conditions [10–13]. Consequently, treatment guidelines generally do not make specific recommendations for aged patients based on comorbid conditions [14,15] and individual treatment choices are typically based on subjective clinical judgment alone.

In this study, we sought to improve the evidence available to guide treatment of elderly lung cancer patients by investigating the impact of CVDs on lung cancer survival using a large population-based dataset of older U.S. adults.

2. Data and methods

2.1. Data

A retrospective cohort study of patients diagnosed with non-small cell lung cancer (NSCLC) was performed using data from the Surveillance, Epidemiology, and End Results (SEER) registry linked to U.S. Medicare administrative claim files (SEER-Medicare). From the entire lung cancer cohort, the patients aged 65+ years old and identified as having a NSCLC histological type (codes are listed in Table 1) were selected. The following additional inclusion criteria were used: (1) lung cancer diagnosed in 1992–2007; (2) patients had health insurance coverage by Medicare Parts A and B and no HMO insurance in each month of the period from 12 months before and 6 months after the diagnosis; (3) the 6th edition AJCC stage not classified as "unknown"; (4) the date of lung cancer onset identified from Medicare trajectories analysis [16] fell into the period not earlier than two and not later than three months from the date of cancer diagnosis recorded by the SEER; and (5) patient's death did not occur earlier than 1 month after NSCLC diagnosis. The ICD-9 codes of CVDs and 78 non-CVD comorbid diseases are listed in Tables 1 and A.1. Treatments with chemotherapy, radiation therapy, and surgery were constructed using ICD-9, CPT/HCPCS, and revenue centers procedure codes from various Medicare sources as previously described [17].

2.2. Ethics statement

All analyses were designed and performed in accordance with the ethical standards of the responsible committee on human experimentation and the Helsinki Declaration (of 1975, revised in 1983) and have been approved by Duke University Health System Institutional Review Board.

2.3. Methods

We studied the impacts of seven CVDs on overall 5-year survival of patients with NSCLC in cancer stage- and treatment-specific groups. The presence of comorbid diseases was evaluated at a baseline (6 months before lung cancer diagnoses) and during a follow-up period of 6 months after diagnosis. First, stage- and treatment-specific effects on survival were analyzed for each CVD using Cox regression in univariable analysis, controlling by age and TN-status. Then, a multivariable analysis was performed additionally controlling for the presence of 84 other comorbid conditions.

Because multiple CVDs often coexist in the same patient, stage- and treatment-specific HRs of the effects of possible combinations of CVDs on patients survival (i.e., a total of 128 while given seven individual CVDs considered) were further evaluated comparing to the survival of patients with NSCLC without a single comorbid CVD. Combinations of CVDs that occurred less often than 0.1% were excluded from the analysis.

The SAS 9.3 statistical package (SAS Institute, Cary, NC) was used for statistical analysis.

2.4. Sensitivity analysis

Using different Medicare sources can result in different estimations of CVDs prevalence, therefore, we tested the results obtained in the main analysis for their stability in the following scenarios for identification of baseline and follow-up CVD prevalence: (1) only inpatient records were used (reflect the most severe conditions), (2) inpatient and outpatient records were used; and (3) a confirmation of CVD diagnosis by a second record was required. The same design as in the main study (univariable, multivariable, and combinations of CVDs analyses) was used, and the sensitivity analysis results were compared with the main study.

3. Results

The characteristics of the patients who met the inclusion criteria are presented in Table 1. Overall, 95,167 patients (54.0% males and 46.0% females) were analyzed, with 50.7% of patients having advanced (stages IIIB and IV) lung cancer. The patients aged 65–69 years old in this study more often had stage IV than early stage cancer ($p < 0.001$), while those aged over 75 years old had stage IV less often ($p < 0.001$) than their younger counterparts. The prevalence of CVD comorbidities was lower at advanced NSCLC ($p < 0.001$), which is, at least partly, explained by the stage IV subgroup containing a higher percentage of younger patients who likely had fewer comorbidities than older patients.

The frequencies of different treatment modalities used are shown in Table 1: among other treatments, surgery was more often used in patients with stage I (57.6%) and II (34.3%), while the combination of chemotherapy and radiotherapy was used most often in stage IIIA (33.4%), IIIB (33.1%) and IV (34.0%). The prevalence of untreated patients increased with advancing stage: from 11.2% (stage I) and 6.6% (stage II) to 22.0% (stage IIIB) and 22.6% (stage IV). Among the studied comorbidities, arterial hypertension (57.7–61.8%, depending on cancer stage) and hyperlipidemia (40.0–46.2%) were the most prevalent in lung cancer patients, followed by other than myocardial infarction (MI) ischemic heart disease (OIHD) (30.4–36.8%) and cardiac arrhythmias (25.6–30.9%) (see Table 1).

Most of CVD comorbidities were associated with decreased survival. For example, heart failure (HF) at baseline significantly decreased overall survival for treatments involving surgery (alone and in combination with other therapies) (HR = 1.35–1.38, stages I and IIIA) and for chemotherapy and radiotherapy (HR = 1.13–1.29 in multivariable analysis, except of stage II) (Table 2, multivariable analysis). Cardiac arrhythmias had the most pronounced effects on survival after chemotherapy with radiotherapy (HR = 1.12–1.15, stages I and IIIA). In contrast, arterial hypertension and hyperlipidemia were observed to have "protective" effects on survival: HR = 0.87–0.94 for surgery, stages I–II, and HR = 0.88–0.93 for radiotherapy, stages I and IV – for hypertension, and HR = 0.85 for surgery, stages I–II, HR = 0.85–0.94 for chemotherapy, stages I, IIIB, and IV, HR = 0.83–0.84 for radiotherapy, stages I and IIIB, and HR = 0.73–0.94 for combination of chemotherapy and radiotherapy, stages II–IV – for hyperlipidemia.

These survival effects persisted and became more pronounced when CVDs were diagnosed during the follow-up period (Table 3). HF significantly increased the risk of death after surgery (HR = 1.70–1.85 in multivariable analysis) and chemotherapy and radiotherapy (HR = 1.13–1.75). MI and cardiac