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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

Table 1
Characteristics of patients with non-small cell lung cancer (NSCLC)[a] and cardiovascular comorbidities, number of patients (%).

Variable	Non-small cell lung cancer stage					
	Stage I (n = 29,836)	Stage II (n = 5133)	Stage IIIA (n = 11,884)	Stage IIIB (n = 18,020)	Stage IV (n = 30,294)	All stages (n = 95,167)
Sex						
Males	15,017 (50.3%)	2854 (55.6%)	6765 (56.9%)	10,167 (56.4%)	16,627 (54.9%)	51,430 (54.0%)
Females	14,819 (49.7%)	2279 (44.4%)	5119 (43.1%)	7853 (43.6%)	13,667 (45.1%)	43,737 (46.0%)
Race						
White	27,997 (93.8%)	4848 (94.4%)	10,971 (92.3%)	16,409 (91.1%)	27,741 (91.6%)	87,966 (92.4%)
African-American	1839 (6.2%)	285 (5.6%)	913 (7.7%)	1611 (8.9%)	2553 (8.4%)	7201 (7.6%)
Age						
65–69 years old	6200 (20.8%)	1267 (24.7%)	2660 (22.4%)	3641 (20.2%)	7014 (23.2%)‡	20,782 (21.8%)
70–74 years old	8874 (29.7%)	1622 (31.6%)	3549 (29.9%)	5156 (28.6%)	9008 (29.7%)#	28,209 (29.6%)
75–79 years old	8100 (27.1%)	1339 (26.1%)	3144 (26.5%)	4593 (25.5%)	7790 (25.7%)‡	24,966 (26.2%)
80–84 years old	4788 (16.0%)	690 (13.4%)	1797 (15.1%)	3042 (16.9%)	4553 (15.0%)†	14,870 (15.6%)
85+ years old	1874 (6.3%)	215 (4.2%)	734 (6.2%)	1588 (8.8%)	1929 (6.4%)†	6340 (6.7%)
Comorbid cardiovascular diseases						
Arterial hypertension (ICD-9 codes 401–405)	18,450 (61.8%)	3098 (60.4%)	6860 (57.7%)	10,687 (59.3%)	17,993 (59.4%)‡	57,088 (60.0%)
Acute myocardial infarction (ICD-9 code 410)	1033 (3.5%)	149 (2.9%)	357 (3.0%)	648 (3.6%)	835 (2.8%)‡	3022 (3.2%)
Old myocardial infarction (ICD-9 code 412)	1809 (6.1%)	305 (5.9%)	621 (5.2%)	995 (5.5%)	1479 (4.9%)‡	5209 (5.5%)
Other ischemic heart disease (ICD-9 codes 411, 413, 414)	10,966 (36.8%)	1797 (35.0%)	3909 (32.9%)	6178 (34.3%)	9224 (30.4%)‡	32,074 (33.7%)
Cardiac arrhythmias (ICD-9 codes 426, 427)	9220 (30.9%)	1489 (29.0%)	3250 (27.3%)	5517 (30.6%)	7770 (25.6%)‡	27,246 (28.6%)
Heart failure (ICD-9 code 428)	5151 (17.3%)	722 (14.1%)	1972 (16.6%)	3977 (22.1%)	4804 (15.9%)†	16,626 (17.5%)
Hyperlipidemia (ICD-9 codes 440, 272)	13,276 (44.5%)	2370 (46.2%)	4942 (41.6%)	7199 (40.0%)	12,750 (42.1%)‡	40,537 (42.6%)
Lung cancer treatment						
Surgery only	17,197 (57.6%)	1759 (34.3%)	1188 (10.0%)	1073 (6.0%)	536 (1.8%)	21,753 (22.9%)
Surgery before radiotherapy	845 (2.8%)	706 (13.8%)	779 (6.6%)	346 (1.9%)	193 (0.6%)	2869 (3.0%)
Surgery before chemotherapy	974 (3.3%)	521 (10.2%)	352 (3.0%)	299 (1.7%)	267 (0.9%)	2413 (2.5%)
Surgery before radio- and chemotherapy	376 (1.3%)	426 (8.3%)	655 (5.5%)	387 (2.1%)	276 (0.9%)	2120 (2.2%)
Radiotherapy only	3395 (11.4%)	400 (7.8%)	2099 (17.7%)	2859 (15.9%)	4581 (15.1%)	13,334 (14.0%)
Radiotherapy before surgery	382 (1.3%)	85 (1.7%)	96 (0.8%)	53 (0.3%)	44 (0.1%)	660 (0.7%)
Radiotherapy before surgery before chemotherapy	29 (0.1%)	16 (0.3%)	28 (0.2%)	22 (0.1%)	32 (0.1%)	127 (0.1%)
Chemotherapy only	717 (2.4%)	115 (2.2%)	839 (7.1%)	2821 (15.7%)	7089 (23.4%)	11,581 (12.2%)
Chemotherapy before surgery	204 (0.7%)	67 (1.3%)	128 (1.1%)	76 (0.4%)	54 (0.2%)	529 (0.6%)
Chemotherapy before surgery before radiotherapy	11 (0.04%)	20 (0.4%)	57 (0.5%)	20 (0.1%)	23 (0.1%)	131 (0.1%)
Chemo- and radiotherapy	2243 (7.5%)	613 (11.9%)	3975 (33.4%)	5968 (33.1%)	10,302 (34.0%)	23,101 (24.3%)
Chemo- and radiotherapy before surgery	128 (0.4%)	66 (1.3%)	249 (2.1%)	128 (0.7%)	65 (0.2%)	636 (0.7%)
No treatment	3335 (11.2%)	339 (6.6%)	1439 (12.1%)	3968 (22.0%)	6832 (22.6%)	15,913 (16.7%)

[a] Histotypes codes for NSCLC: 8046/3, 8140/3, 8141/3, 8143/3, 8147/3, 8250/3, 8251/3, 8252/3, 8253/3, 8254/3, 8255/3, 8260/3, 8310/3, 8323/3, 8480/3, 8481/3, 8570/3, 8571/3, 8572/3, 8573/3, 8574/3, 8576/3, 8052/3, 8070/3, 8071/3, 8072/3, 8073/3, 8074/3, 8075/3, 8076/3, 8078/3, 8012/3, 8013/3, 8014/3, 8123/3, 8082/3, 8310/3, 8003/3, 8004/3, 8005/3, 8011/3, 8015/3, 8022/3, 8030/3, 8031/3, 8032/3, 8033/3, 8034/3, 8035/3, 8120/3, 8121/3, 8122/3, 8123/3, 8124/3, 8200/3, 8201/3, 8320/3, 8430/3, 8490/3, 8510/3, 8550/3, 8551/3, 8560/3, 8562/3, 8249/3, 8240/3, 8241/3, 8242/3, 8243/3, 8244/3, 8245/3, 8246/3. These histotypes were classified using the International Classification of Diseases for Oncology, the 3rd revision (ICD-O-3), with comparison for equivalency to ICD-O-2 codes for lung cancer cases diagnosed before 2001.
†, ‡, # Shows p-values of the comparison of frequencies for stage IV vs. stages I + II as follows: ‡ $p < 0.001$, † $0.001 < p < 0.05$; # $p > 0.05$, all for the given category of variables (i.e., using the values in the given line only).

arrhythmias also decreased survival after surgery (HR = 1.36–1.96 and HR = 1.44–1.63, respectively) and chemotherapy and radiotherapy (HR = 1.26–1.94 and HR = 1.15–1.67, respectively). For arterial hypertension, a "protective" effect remained for untreated patients (HR = 0.82–0.85), but it worsened survival of patients who received surgery or chemotherapy with radiotherapy (HR = 1.10–1.28). Most of these effects became less pronounced among the patients with stage IV cancer. The "protective" effect of hyperlipidemia remained stable for various treatments (HR = 0.79–0.89).

The effects of specific groups of CVD comorbidities on patients' survival are presented in Table 4. Having multiple CVDs significantly increased mortality for stage I–II patients who had surgery (e.g., for OIHD + arrhythmia + HF at stage I HR = 2.05, 95% CI 1.57–2.67, $p < 0.001$) or had chemotherapy with radiotherapy at all stages (e.g., for hypertension + HF at stage IIIA HR = 2.20, 95% CI 1.63–2.98, $p < 0.001$). A synergistic effect was observed for multiple combinations of CVDs, where the resulting effect of combination was higher than the effect obtained by multiplying the HRs of each individual CVD calculated in multivariable analyses with 7 CVDs. These effects were more often observed for surgery at stages I and II cancer and for chemotherapy with radiotherapy at all stages (see Table 4). For example, the combined effect of combination OIHD + arrhythmia + HF for surgery at stage I (HR = 2.05, 95% CI 1.57–2.67, $p < 0.001$) and for chemotherapy with radiotherapy at stage IIIB (HR = 2.10, 95% CI 1.54–2.87, $p < 0.001$) was higher than respective multiplied effects (HR = 1.51 and HR = 1.23, $p < 0.05$, respectively).

Sensitivity analysis confirmed the stability of the results (see Appendix: Tables 3A.1 and 3A.2). In general, inpatient-based analysis showed slightly higher HRs for MI, HF, and arrhythmias at

Table 2
The effects of cardiovascular comorbidities at baseline on survival of lung cancer patients, cancer stage and treatment specific.

CVD comorbidity	Type of analysis: uni- and multivariable	Stage I			Stage II			Stage IIIA			Stage IIIB			Stage IV		
		Surgery only	Radiotherapy only	Chemotherapy+ radiotherapy	Surgery only	Surgery before radiotherapy and chemotherapy	Chemotherapy + radiotherapy	Surgery only	Chemotherapy only	Chemotherapy + radiotherapy	Chemotherapy only	Radiotherapy only	Chemotherapy + radiotherapy	Chemotherapy only	Radiotherapy only	Chemotherapy + radiotherapy
Arterial hypertension	Uni	1.01	0.92*	1.00	0.93	1.15	1.00	0.99	1.09	1.04	0.96	1.02	1.05	1.05*	0.99	1.04#
	Multi	0.94*	0.88*	0.95	0.87*	1.16	0.92	0.95	1.12	1.00	0.92	0.98	0.99	1.02	0.93*	0.98
Myocardial infarction	Uni	1.37**	1.31*	1.36*	1.18	0.52	0.99	1.96**	1.54*	1.30*	0.93	1.25*	1.08	1.21*	1.36*	1.16*
	Multi	1.12	1.18	1.08	1.06	0.61	0.83	1.82*	1.75*	1.01	0.83	1.13	0.91	1.04	1.27*	1.03
Other ischemic heart disease	Uni	1.21**	1.05	1.26**	1.09	1.06	1.06	1.22*	1.12	1.17**	1.05	1.05	1.13**	1.15**	1.04	1.08**
	Multi	1.06*	0.95	1.18*	1.02	1.13	0.90	1.17	1.16	1.07	0.98	0.95	1.01	1.08*	0.97	1.01
Old myocardial infarction	Uni	1.20**	1.01	1.26*	0.93	0.76	1.37	1.34*	1.06	1.14	1.39**	1.05	1.16*	1.05	1.04	1.08
	Multi	0.99	0.96	1.02	0.85	0.85	1.39	1.07	0.90	1.02	1.38**	0.96	1.09	0.92	0.98	1.03
Cardiac arrhythmia	Uni	1.20**	1.14*	1.32**	1.09	1.24	1.15	1.11	1.18*	1.26**	1.12*	1.19**	1.18**	1.11**	1.09*	1.13**
	Multi	1.05	1.05	1.15*	1.04	1.20	1.06	1.03	1.10	1.12*	1.09	1.10	1.05	1.00	1.05	1.04
Heart failure	Uni	1.60**	1.33**	1.24**	1.23*	1.75**	1.28*	1.55**	1.20	1.42**	1.14*	1.15*	1.30**	1.29**	1.02	1.24**
	Multi	1.35**	1.29**	1.04	1.11	1.51	1.04	1.38*	1.10	1.22**	1.04	1.04	1.15**	1.20**	0.99	1.13**
Hyperlipidemia	Uni	0.89**	0.86**	0.92	0.85*	1.10	0.82*	0.94	0.85*	0.93*	0.93	0.90*	0.97	0.97	1.01	0.96*
	Multi	0.85**	0.83**	0.85*	0.85*	1.05	0.73*	0.91	0.85	0.88*	0.91*	0.84**	0.94*	0.94*	1.01	0.93*

* $0.001 < p < 0.05$.
** $p < 0.001$.
§ $0.05 < p < 0.3$.

Table 3
The effects of cardiovascular comorbidities occurring during follow-up (i.e., calculated versus the absence of specific CVD both at baseline and during follow-up) on survival of lung cancer patients, cancer stage and treatment specific.

CVD comorbidity	Type of analysis: uni- and multivariable	Stage I			Stage II			Stage IIIA			Stage IIIB			Stage IV		
		Surgery only	Radiotherapy only	Chemotherapy + radiotherapy	Surgery only	Surgery before radiotherapy and chemotherapy	Chemotherapy + radiotherapy	Surgery only	Chemotherapy only	Chemotherapy + radiotherapy	Chemotherapy only	Radiotherapy only	Chemotherapy+ radiotherapy	Chemotherapy only	Radiotherapy only	Chemotherapy + radiotherapy
Arterial hypertension	Uni	1.00	0.94	0.91	1.13	1.46	1.21	0.80	0.96	0.86*	0.92	0.93	0.97	0.95	1.08	0.97
	Multi	1.18**	1.06	1.02	1.28*	1.42	1.09	0.92	0.87	1.04	1.08	0.99	1.10*	0.98	0.99	1.01
Myocardial infarction	Uni	1.28**	1.50**	1.49*	0.87	0.81	1.91	1.29	1.52	1.20	1.27*	1.26	1.32**	0.99	1.13	1.15*
	Multi	1.89**	1.66**	1.94**	1.36*	1.96*	1.62*	1.78**	1.52*	1.62**	1.48**	1.41*	1.69**	1.30**	1.09	1.26**
Other ischemic heart disease	Uni	1.02	0.94	1.02	0.94	1.33	0.56*	0.87	0.97	1.01	0.95	0.97	0.90*	0.90*	0.76**	0.90*
	Multi	1.36**	1.12	1.18*	1.12	1.37	0.87	1.34*	1.00	1.18*	1.21*	1.16*	1.11*	1.01	0.82*	1.00
Old myocardial Infarction	Uni	0.89*	0.91	1.05	0.96	0.76	1.35	1.21	0.72	1.12	0.73*	0.87	0.92	0.90	1.01	0.99
	Multi	1.24**	1.25*	1.27*	1.05	1.32	1.00	1.46*	1.38	1.35**	0.84	1.03	1.09	1.07	0.96	1.07
Cardiac arrhythmia	Uni	1.07*	1.13	1.29**	1.32*	1.27	1.31	1.37*	1.30	1.33**	1.44**	1.29**	1.28**	1.22**	1.16*	1.18**
	Multi	1.44**	1.43**	1.61**	1.63**	1.21	1.33*	1.57**	1.52**	1.63**	1.67**	1.52**	1.52**	1.44**	1.15*	1.27**
Heart failure	Uni	1.15**	1.34**	1.14	1.28*	1.75	2.02**	1.34*	1.29	1.25**	1.26**	1.06	1.27**	1.23**	1.09	1.16**
	Multi	1.75**	1.59**	1.43**	1.70**	1.59*	1.64**	1.85**	1.75**	1.66**	1.55**	1.31**	1.64**	1.48**	1.13*	1.31**
Hyperlipidemia	Uni	0.84**	0.82*	0.67**	0.83	0.63	0.62*	0.76*	0.93	0.87	0.96	0.82*	0.80**	0.84*	0.82*	0.87*
	Multi	0.95	0.93	0.79*	0.85	1.01	0.83	0.86	1.01	0.96	0.96	0.96	0.90	0.87*	0.80**	0.89*

* $0.001 < p < 0.05$.
** $p < 0.001$.
§ $0.05 < p < 0.3$.

Table 4
Combinations of co-existed cardiovascular comorbidities in lung cancer patients (for stage and treatment specific groups) at a baseline that increase risk significantly higher than summarized HRs (95% CI) of each disease in the combination.

Combinations of CVDs	Stage I			Stage II	Stage IIIA	Stage IIIB			Stage IV		
	Surgery only	Radiotherapy only	Chemotherapy + radotherapy	Surgery only	Chemotherapy + radiotherapy	Chemotherapy only	Radiotherapy only	Chemotherapy + radiotherapy	Chemotherapy only	Radiotherapy only	Chemotherapy + radiotherapy
HF + ARR	1.62* 1.20–2.20	1.56* 1.08–2.25	2.18*,† 1.32–3.61	1.39 0.51–3.78	1.96* 1.19–3.22	1.14 0.77–1.68	1.09 0.77–1.55	1.05 0.78–1.43	1.53* 1.06–2.20	0.91 0.63–1.31	1.42* 1.06–1.90
HP + Lip	0.90*,† 0.82–0.99	0.78* 0.66–0.91	0.89 0.74–1.07	0.73* 0.58–0.92	0.96 0.84–1.08	0.89 0.76–1.03	0.92 0.78–1.08	0.95 0.86–1.05	0.98 0.90–1.06	0.97 0.87–1.09	0.96 0.90–1.03
HP + HF	1.34* 1.04–1.71	1.35* 1.06–1.71	0.98 0.68–1.41	0.83 0.45–1.52	2.20**,† 1.63–2.98	1.07 0.79–1.46	1.04 0.78–1.37	1.48*,† 1.17–1.88	1.35* 1.10–1.67	0.88 0.68–1.14	1.49**,† 1.23–1.82
HP + ARR	1.05 0.92–1.20	1.08 0.86–1.36	1.35* 1.01–1.80	0.97 0.71–1.33	1.20 0.98–1.49	1.20 0.96–1.50	1.48**,† 1.19–1.84	1.24*,† 1.06–1.45	1.01 0.87–1.18	1.05 0.89–1.24	1.13* 1.00–1.28
HP + OIHD	1.06 0.92–1.21	0.94 0.75–1.17	1.14 0.86–1.50	0.78 0.54–1.13	1.36*,† 1.13–1.64	0.92 0.71–1.18	0.86 0.68–1.08	1.14 0.97–1.35	1.24* 1.06–1.46	1.01 0.85–1.19	1.08 0.95–1.22
OIHD + Lip	0.94 0.79–1.13	0.86 0.64–1.16	1.08 0.73–1.60	1.00 0.68–1.46	1.05 0.81–1.36	1.10 0.83–1.45	0.84 0.59–1.18	0.95 0.76–1.19	1.02 0.84–1.25	1.03 0.79–1.34	1.03 0.89–1.20
OIHD + HF	1.63* 1.15–2.32	1.52* 1.01–2.29	0.57 0.28–1.14	2.89*,† 1.27–6.57	1.75* 1.16–2.63	1.64* 1.01–2.67	1.74*,† 1.04–2.92	1.52* 1.04–2.23	1.21 0.80–1.82	0.92 0.61–1.36	1.48* 1.04–2.09
OIHD + ARR	1.14 0.92–1.41	1.34 0.96–1.87	1.83* 1.26–2.64	0.94 0.59–1.51	1.33 0.97–1.83	1.27 0.84–1.92	1.37* 1.01–1.85	1.25 0.95–1.65	1.12 0.87–1.44	1.00 0.71–1.40	1.06 0.85–1.32
OIHD + ARR + Lip	1.06 0.83–1.36	0.90 0.56–1.43	1.59* 1.02–2.48	0.84 0.41–1.71	0.85 0.57–1.26	1.01 0.60–1.69	0.79 0.47–1.33	0.96 0.70–1.32	1.06 0.80–1.39	1.27 0.88–1.83	1.15 0.92–1.43
OIHD + ARR + HF	2.05**,† 1.57–2.67	1.19 0.82–1.72	1.95* 1.14–3.33	1.98 0.97–4.05	1.54 0.98–2.44	2.01*,† 1.20–3.36	1.16 0.74–1.82	2.10**,† 1.54–2.87	1.36 0.96–1.94	1.27 0.81–2.00	1.05 0.72–1.54
HP + HF + Lip	1.24 0.96–1.62	0.80 0.55–1.16	0.90 0.59–1.38	0.92 0.47–1.80	1.24 0.85–1.81	0.92 0.69–1.24	0.78 0.51–1.18	1.25 0.96–1.62	1.19 0.95–1.49	0.85 0.63–1.14	1.18 0.95–1.47
HP + ARR + Lip	0.87* 0.76–1.00	0.92 0.70–1.21	0.88 0.60–1.28	1.22·† 0.89–1.68	1.23*,† 1.00–1.51	1.13 0.90–1.41	0.92 0.68–1.25	1.18·† 0.99–1.41	0.98 0.86–1.13	1.07 0.88–1.29	1.03 0.91–1.17
HP + ARR + HF	1.33* 1.04–1.70	1.18 0.88–1.59	1.21 0.84–1.73	1.04 0.59–1.82	1.90** 1.36–2.65	1.47*,† 1.05–2.05	1.21 0.89–1.64	1.54**,† 1.20–1.97	1.39* 1.06–1.81	1.22 0.88–1.67	1.26* 1.02–1.56
HP + OIHD + Lip	0.90 0.80–1.01	0.88·† 0.72–1.08	1.05 0.85–1.28	0.95 0.73–1.23	0.94 0.80–1.11	1.06 0.88–1.28	0.90 0.72–1.13	1.08·† 0.95–1.23	1.02 0.91–1.14	0.88 0.74–1.04	1.01 0.92–1.11
HP + OIHD + HF	1.24 0.97–1.58	1.47*,† 1.10–1.96	1.26 0.85–1.87	2.07*,† 1.15–3.72	1.31 0.92–1.86	1.06 0.78–1.44	1.08 0.79–1.49	1.22 0.94–1.58	1.35* 1.01–1.79	0.76 0.56–1.04	1.11 0.89–1.38
HP + OIHD + ARR	1.20* 1.03–1.39	1.03 0.78–1.35	1.39 1.00–1.94	1.06 0.71–1.58	1.42* 1.08–1.87	0.93 0.66–1.30	0.93 0.70–1.24	1.27* 1.03–1.56	1.07 0.87–1.32	0.90 0.71–1.15	1.12 0.96–1.30
HP + ARR + HF + Lip	1.41* 1.08–1.83	1.02 0.64–1.63	1.30 0.83–2.05	1.12 0.50–2.53	1.26 0.88–1.81	0.89 0.60–1.33	0.87 0.59–1.27	1.42* 1.07–1.87	1.26 0.98–1.62	0.87 0.60–1.24	1.19 0.93–1.52
HP + OIHD + Lip + OIMI	0.89 0.69–1.15	0.71 0.45–1.12	1.59·† 0.99–2.56	0.74 0.43–1.28	1.21 0.84–1.73	1.39 0.90–2.16	1.13 0.66–1.92	1.06 0.80–1.41	1.00 0.78–1.29	1.42·† 0.99–2.05	0.90 0.73–1.10
HP + OIHD + HF + Lip	1.43**,† 1.17–1.76	1.14 0.88–1.48	1.16 0.85–1.59	1.04 0.62–1.73	1.57*,† 1.19–2.08	1.18·† 0.89–1.58	1.14 0.82–1.58	1.45**,† 1.17–1.80	1.16 0.97–1.40	0.90 0.69–1.19	1.14 0.97–1.35
HP + OIHD + ARR + Lip	0.99 0.87–1.13	0.72* 0.56–0.94	0.99 0.73–1.34	0.76 0.55–1.04	1.06 0.86–1.30	1.01 0.80–1.28	1.12 0.86–1.47	1.19*,† 1.00–1.41	1.07 0.92–1.24	1.06 0.88–1.29	1.12·† 0.98–1.27

Table 4 (*Continued*)

Combinations of CVDs	Stage I			Stage II	Stage IIIA	Stage IIIB			Stage IV		
	Surgery only	Radiotherapy only	Chemotherapy + radiotherapy	Surgery only	Chemotherapy + radiotherapy	Chemotherapy only	Radiotherapy only	Chemotherapy + radiotherapy	Chemotherapy only	Radiotherapy only	Chemotherapy + radiotherapy
HP + OIHD + ARR + HF	1.91**,† 1.60–2.27	1.32* 1.04–1.67	1.84**,† 1.37–2.47	1.14 0.60–2.15	2.10**,† 1.57–2.81	1.09 0.78–1.53	1.60**,† 1.24–2.05	1.43** 1.16–1.76	1.57** 1.23–1.99	1.24† 0.95–1.63	1.24* 1.01–1.52
HP + OIHD + HF + Lip + OIMI	2.10**,† 1.48–2.97	1.00 0.60–1.68	0.90 0.44–1.81	3.60*,† 0.89–14.5	1.31 0.80–2.15	1.41 0.77–2.57	0.77 0.38–1.55	1.84*,† 1.19–2.83	0.82 0.52–1.30	0.93 0.55–1.57	1.25 0.83–1.87
HP + OIHD + ARR + Lip + OIMI	1.19† 0.90–1.56	0.79 0.46–1.37	0.70 0.36–1.37	0.54 0.24–1.21	1.63 1.00–2.68	1.30 0.76–2.22	0.71 0.37–1.38	0.87 0.57–1.32	1.25 0.90–1.71	1.29 0.75–2.24	1.27 0.97–1.65
HP + OIHD + ARR + HF + Lip	1.58**,† 1.36–1.84	0.94 0.73–1.20	1.38* 1.05–1.80	0.90 0.58–1.40	1.37* 1.06–1.77	0.96 0.75–1.22	1.27*† 0.97–1.64	1.18 0.98–1.41	1.48**,† 1.25–1.76	1.07 0.82–1.40	1.32**,† 1.12–1.56
HP + OIHD + ARR + HF + Lip + OIMI	1.99**,† 1.53–2.57	1.27 0.81–1.98	1.78* 1.02–3.10	1.42 0.63–3.22	1.46 0.90–2.36	2.59**,† 1.65–4.07	0.96 0.60–1.56	1.36 0.95–1.93	1.45* 1.00–2.10	0.91 0.55–1.49	1.44* 1.03–2.00

Note that CVDs- and treatment-specific effects are not shown in this table when had more than 70% of cells in the row/column that had ≤20 observed cases in a cell.
CVD, cardiovascular disease; HP, arterial hypertension; HF, heart failure; MI, myocardial infarction; OIMI, old myocardial infarction; OIHD, other ischemic heart disease; ARR, cardiac arrhythmia; Lip, hyperlipidemia.
* $0.001 < p < 0.05$.
** $p < 0.001$.
† The impact is significantly higher for combination of CVDs than for multiplied effects of each separate CVD in this combination.
§ $0.05 < p < 0.3$.

follow-up. That may be explained by the stronger effects of more severe CVDs detected during the hospital stay and by more sever impacts of comorbid CVDs on survival of hospitalized lung cancer patients who likely have more deteriorated health status than their non-hospitalized counterparts. Also, the effects of HF and MI on survival in the diagnosis confirmation scenario were slightly higher than in main analysis, especially at follow-up.

4. Discussion

The relatively high prevalence of CVD comorbidity among the patients with NSCLC was observed in multiple studies that involved older patients [4,8,18]. However, to the best of our knowledge this study is novel in the analysis of the impact of a wide spectrum of CVDs (both alone and in combinations) in a stage and treatment-specific manner. Considering CVDs in combination is clearly important and relevant because several comorbid conditions may have a multiplicative rather than additive effect on cancer survival: focusing only on a certain number of diseases or on the most severe comorbid condition may miss the burden of multiple diseases on prognosis of survival [18]. In general, the prevalence of some specific CVDs in older NSCLC patients in our study were higher than what has been reported by other studies [9,19,20]; this discussed in detail for each disease below.

4.1. Arterial hypertension

The arterial hypertension prevalence in our study was 60.0%, that is higher than reported in other studies, e.g., 12% prevalence in lung cancer patients aged 65+ years old [9] and 24% in patients aged 70+ years old [20]. These previously reported numbers are more consistent with the results of our sensitivity analysis obtained for inpatient records – i.e., 26.1% (Table 2A). In our study, having arterial hypertension at baseline or in non-treated patients at follow-up improved patients' survival. That might be, at least partly, due to the effects of certain anti-hypertensive treatments. For example, in other studies angiotensin I converting enzyme and angiotensin II type 1 receptor blockers (that mainly control arterial hypertension) were negatively correlated with cancer incidence [21,22], suggesting a potential anti-proliferative effect on tumor cells and/or their microenvironment [23]. Also, other studies investigated the peri-treatment effects of arterial hypertension on survival: for example, arterial hypertension onset during the treatment of advanced NSCLC with the monoclonal antibody bevacizumab (a monoclonal antibody that targets vascular endothelial growth factor) in combination with carboplatin and paclitaxel was associated with improved outcomes [24]. From other side, bevacizumab, even being associated with improved outcomes in patients with NSCLC, could increase the risk of such complications as arterial thrombo-embolic events, arterial hypertension, and heart failure, especially in patients with pre-existing CVD who are older than 65 years old and have a history of a prior thromboembolic event [25,26]. In our study, arterial hypertension at follow-up did not improve survival of patients on chemotherapy.

4.2. Heart failure

The HF prevalence in our study (17.5%) was higher than those described in non-Medicare based studies (5.6–8.4%) [5], being in agreement with our inpatients results (7.2%). Previous studies pointed that prognostic significance of HF for cancers, including lung cancer, was underestimated [27]. In our study, HF decreased survival of lung cancer patients treated with surgery and chemotherapy and radiotherapy, consistent with other studies that showed that HF was a significant predictor (OR = 6.0) of operative mortality among elderly lung cancer patients [28]. Also, HF was

reported with high frequency in patients with NSCLC treated with a widely prescribed for cancer treatment doxorubicin [29].

4.3. Cardiac arrhythmias

28.6% lung cancer patients in our study had cardiac arrhythmias. Arrhythmias significantly impacted patient survival, especially among those who had surgery or chemotherapy with radiotherapy. Previous studies have generally not investigated the impact of pre-existing arrhythmias but rather their risks of occurring immediately following lung cancer surgery [30]. For example, supraventricular arrhythmias have been shown to occur in 10–28% of patients after pulmonary resection [31–33]. Although post-operative arrhythmias – mostly atrial fibrillation – are recognized, the arrhythmias are not commonly listed among typical adverse cardiotoxic effects. Although the relationship between chemotherapy and cardiac arrhythmias remain not well established, several classes of chemotherapeutic agents appear to be associated with arrhythmia (e.g., cisplatin, anthracyclines, 5-FU, melphalan, dispeptide) [34]. In our study, arrhythmias significantly decreased the survival of NSCLC patients after surgery and among patients treated by chemotherapy alone or in combination with radiotherapy at all cancer stages. For radiation therapy, the literature supports the evidence of heart toxicity after radiotherapy to the chest (e.g., among breast cancer and Hodgkin's lymphoma patients) [35]; however, the data on arrhythmias are very sparse. In our study, the occurrence of cardiac arrhythmia during follow-up period decreased the survival of lung cancer patients who did not have arrhythmias before the beginning of cancer treatment.

4.4. Myocardial infarction

In our study, 3.2% of patients had MI 6 months before or after cancer diagnosis and 5.5% had an old MI. That is generally in agreement with a previous study of thoracotomy patients where 12.1% had angina or past MI [36]. However, our numbers are lower than some studies with self-reported MI, such as a study where 22% of females aged 70+ years old who underwent pulmonary resection for NSCLC had an MI history [37]. In our study, MI significantly impacted survival of lung cancer patients, especially of those who underwent surgery, which is consistent with previous studies showed that prior MI (OR = 4.3) was a significant predictor of operative mortality among elderly lung cancer patients [28] and that acute MI strongly associated with peri-operative mortality of stage I-IIIA lung cancer patients [38].

4.5. Hyperlipidemia

The role of hyperlipidemia in survival of cancer patients has been discussed previously, but never studied at a large population level. Pooled analysis of six prospective coronary heart disease studies performed as long as 40 years ago showed significantly lower average cholesterol level among men who died from colon cancer, but the results were inconclusive for other cancer sites, including lung [39]. A cooperative trial in the primary prevention of IHD using clofibrate subsequently showed a higher but not significant number of cancer deaths in the treated group than in the control group [40]. The findings on lipid levels and cancer risk with less than 10-year follow-up have been suggested to reflect the clinical course of the illness and not an etiological link [41]. The mechanism may be inhibition of lipoprotein synthesis or increased lipoprotein catabolism [42–44], though the relatively short course associated with many lung cancer cases makes it unlikely that lipoprotein changes are a powerful factor. Another potential explanation is that medications used to treat hyperlipidemia decrease cancer risk and/or improve cancer survival. For example, some studies have reported that statins decrease cancer risk [45,46], although a meta-analysis of 26 randomized studies did not find that statins significantly reduced cancer incidence (OR 1.02; 95% CI 0.97–1.07) or cancer deaths (OR 1.01; 95% CI 0.93–1.09) [47]. Recently, statins have been reported to be associated with reduced risk of lung cancer [48,49] as well as other cancers. Other studies have suggested that underlying metabolic syndrome dysfunction may be associated with better survival: for example a subgroup of patients with advanced NSCLC who developed hypertriglyceridemia after bexarotene treatment appeared to have better survival (12.3 months) than controls [50]. The beneficial effect of hyperlipidemia observed across stages and treatments in our study requires further investigation which could be attempted with the records on medications that available in Medicare files.

5. Conclusion

This novel study analyzed stage- and treatment-specific effects of various CVD comorbidities on lung cancer survival, while taking into account comorbid conditions of all other organs/systems. The presence of CVD, especially multiple CVDs, substantially impacts the survival of lung cancer patients, particularly for patients with stages I–IIIB, but also (to a less extent) for those with stage IV disease. A better understanding of the effects of CVDs on survival can improve estimates of lung cancer prognosis. It could also help improve treatment selection and ultimately lead to the strategies to enhance overall survival or quality of life in older patients who often have one or more CVDs. The results of these analyses indicate the need for comprehensive evaluation of doses and schedules of chemotherapy and radiotherapy in patients with different CVDs. That could provide further details to appropriate choice of lung cancer treatment that improve survival among older patients with comorbid conditions.

Competing interests

The authors have declared that no competing interests exist.

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Authors contribution

JK, MB, HKL, and IA developed the concept behind the study; JK and IA designed the study and carried out the data analysis with help from MB and KA; JK wrote the paper with help from IA, MB, AY, and KA; HKL and AY provided critical reviews of the manuscript. All authors have read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.lungcan.2015.01.006.

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