

Impact of Pre-Existing Cardiovascular Disease on Treatment Patterns and Survival Outcomes in Patients With Lung Cancer

Atul Batra

Tom Baker Cancer Centre <https://orcid.org/0000-0002-1934-8408>

Dropen Sheka

University of Calgary Cumming School of Medicine

Shiyong Kong

University of Calgary

Winson Y Cheung (✉ winson.cheung@ahs.ca)

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Abstract

Background: Baseline cardiovascular disease can impact the patterns of treatment and hence the outcomes of patients with lung cancer. This study aimed to characterize treatment trends and survival outcomes of patients with pre-existing cardiovascular disease prior to their diagnosis of lung cancer.

Methods: We conducted a retrospective, population-based cohort study of patients with lung cancer diagnosed from 2004 to 2015 in a large Canadian province. Multivariable logistic regression and Cox regression models were constructed to determine the associations between cardiovascular disease and treatment patterns, and its impact on overall and cancer-specific survival, respectively.

Results: A total of 20,689 patients with lung cancer were eligible for the current analysis. Men comprised 55%, and the median age at diagnosis was 70 years. One-third had at least one cardiovascular disease, with the most common being congestive heart failure in 15% of patients. Pre-existing cardiovascular disease was associated with a lower likelihood of receiving chemotherapy (odds ratio [OR], 0.53; 95% confidence interval [CI], 0.48-0.58; $P < .0001$), radiotherapy (OR, 0.76; 95% CI, 0.7-0.82; $P < .0001$), and surgery (OR, 0.56; 95% CI, 0.44-0.7; $P < .0001$). Adjusting for measured confounders, the presence of pre-existing cardiovascular disease predicted for inferior OS (hazard ratio [HR], 1.1; 95% CI, 1.1-1.2; $P < .0001$) and CSS (HR, 1.1; 95% CI, 1.1-1.1; $P < .0001$).

Conclusions: Patients with lung cancer and pre-existing cardiovascular disease are less likely to receive any modality of cancer treatment and have poor OS and CSS. As effective therapies such as immunology drugs are introduced, early cardio-oncology consultation may optimize management and outcomes of lung cancer.

Background

Cardiovascular disease and cancer are the two leading causes of death worldwide, and account for approximately 17.9 million and 9.6 million deaths annually across the globe, respectively(1–3). The relationship between these two comorbid conditions is complex. While cardiovascular disease and cancer share common modifiable risk factors and pathophysiological mechanisms, the treatments and outcomes of one may be affected by the other (4–9). Further, cancer treatments, including chemotherapy, targeted therapy, and radiotherapy, have been associated with increased downstream cardiovascular sequelae, independent of other risk factors(10).

For example, cigarette smoking is estimated to contribute to 71% of lung cancer related mortality and 10% of deaths due to cardiovascular disease, respectively(11). Inflammation and oxidative stress are key mechanisms in the pathophysiology of both conditions(12–14). The other link between lung cancer and cardiovascular disease is advanced age. While half of patients diagnosed with cardiovascular disease are aged more than 60 years, the median age at diagnosis for lung cancer is 70 years(15, 16)

Previous studies have primarily focused on the long-term cardiovascular complications of cancer treatments(17, 18). Data related to the prevalence of pre-existing cardiovascular diseases in patients diagnosed with cancer has been reported to range from 5–43%, depending on the primary site of malignancy and the geographical region where study was conducted (19, 20). However, there are limited studies reporting on the impact of pre-existing cardiovascular disease on subsequent treatment patterns and survival outcomes of lung cancer. A large study of patients with breast cancer concluded that those with baseline cardiovascular disease were less likely to receive any form of therapy (surgery, chemotherapy, hormonal therapy, and radiotherapy) compared to patients without pre-existing cardiovascular comorbidities(21). Further, overall survival but not cancer specific survival was shorter in these patients. While a few studies have described inferior survival outcomes among patients with lung cancer and pre-existing cardiovascular disease, the effect of treatments on prognosis remains largely unknown(22, 23).

In this study, we aimed to identify the proportion of patients who had at least one pre-existing cardiovascular disease at the time of their diagnosis of lung cancer. Further, we analyzed the effect of pre-existing cardiovascular disease on treatment patterns, including chemotherapy, radiation therapy, and surgery, as well as its impact on survival outcomes in patients with lung cancer.

Methods

Data sources and study population

The study was conducted in Alberta, which is a large province in Canada, with a population of over 4 million people and has a single-payer, universal healthcare system. This was a retrospective, population-based study, where we compiled data from various administrative sources including the Alberta cancer registry (ACR), hospital discharge abstracts, national ambulatory care reporting system, provincial physician billing claims, vital statistics, and the 2011 census.

The ACR prospectively records data on all residents diagnosed with cancer in the province, including demographic variables, tumor characteristics, and primary treatment patterns. The discharge abstracts provide data collected during hospital admissions and details up to 25 International Classification of Diseases tenth version (ICD-10) diagnoses and up to 20 procedures coded as per the Canadian Classification of Health Interventions. Likewise, the ambulatory care data records up to 10 diagnoses and 10 procedures, respectively. The provincial physician billing claims data provide the location of healthcare delivery, physician specialty, one procedure code, and up to three ICD-10 diagnoses. Each patient in the province has a unique provincial health number, which was used to link the data from the various sources. Data on death from lung cancer or other causes were retrieved from vital statistics.

Patients aged 18 years and older with a diagnosis of lung cancer between January 1, 2004, and December 31, 2015, in Alberta, Canada were included in the current analysis. Patients who moved out of Alberta within 12 months of primary treatment, those who had multiple primary tumors, or who did not have an Alberta healthcare number were excluded.

Approval was obtained from the Health Research Ethics Board of Alberta's Cancer Committee prior to commencing this study.

Clinical variables and outcomes

Outcomes

The main outcomes of this study were treatment patterns and survival outcomes. We assessed the impact of pre-existing cardiovascular disease on treatments, including the receipt of any chemotherapy, surgery, and radiotherapy. Primary surgery type was identified as the most definitive surgical procedure (lobectomy or segmental resection or pneumonectomy) performed within 1 year of diagnosis. Information on the administration of chemotherapy and radiotherapy was categorized in a binary fashion (yes or no), which was obtained via the ACR. Survival outcomes including overall survival (OS) and cancer specific survival (CSS) were retrieved from vital statistics records.

Independent Variables

Using data from the above sources, the presence of pre-existing cardiovascular disease at or preceding the time of diagnosis of lung cancer was identified using previously validated ICD algorithms(24). Cardiovascular diseases included presence of congestive heart failure, myocardial infarction, cerebrovascular accident and/or, arrhythmias. Tumor characteristics included the American Joint Committee on Cancer stage and histologic type or subtype (adenocarcinoma, squamous cell carcinoma, small cell lung cancer, carcinoid, large cell cancer, and others). The discharge abstracts, physician billing claims, and ambulatory care data were used to derive the Charlson's comorbidity index. Alberta is strategically divided into five health zones for healthcare delivery. Postal code at diagnosis was used to assign each patient to their respective health zone (Calgary, Edmonton, North, Central, or South) and to retrieve neighbourhood-level socioeconomic status (education and income levels) based on the 2011 census. Driving time to the nearest oncology facility was calculated using Google Maps interface and postal codes, and it was further categorized as one, one to two and more than two hours, as per previously published literature(25).

Statistical Analysis

Baseline characteristics were summarized using descriptive statistics, where the Student's t test and Wilcoxon rank-sum test were used to compare continuous variables, and the chi-square tests were applied to compare categorical variables across the different patient groups. Multivariable logistic regression analyses were performed to identify associations between pre-existing cardiovascular disease and receipt of treatment (including chemotherapy, radiotherapy, and surgery). Kaplan-Meier curves were plotted to estimate OS and CSS differences between patients with and without cardiovascular disease, and compared using log rank tests. Cox proportional hazards models were constructed to examine the effect of pre-existing cardiovascular disease on OS and CSS, respectively. OS and CSS were defined as the time interval between the date of cancer diagnosis and the date of death from any cause, and the

date of death from lung cancer, respectively. Subgroup analyses were performed to investigate whether the effects of cardiovascular disease on outcomes were modified by different treatments, including chemotherapy, surgery, and radiotherapy. All tests were two-sided, and the significance level was defined *a priori* as 0.05. All analyses were performed with SAS statistical software version 9.4 (SAS Institute, Inc, Cary, NC).

Results

Patient characteristics

A total of 20,689 patients were diagnosed with lung cancer during the study period. The median age at diagnosis was 70 (interquartile range, 62–78) years, and women constituted 49% of the cohort. Approximately half of patients had distant metastases at diagnosis. Adenocarcinoma (37.3%) and squamous cell carcinoma (17.8%) were the most common histologies, while small cell lung cancer was diagnosed in 12.4%. Surgery was performed in 16.5%, and chemotherapy and radiation therapy were administered in 27.4% and 30.3% of patients, respectively. Only 20 patients (0.1%) received immunotherapy. Additional baseline characteristics are shown in Table 1.

Table 1
Baseline characteristics of patients with lung cancer

Variables	Total (N=20689), n (%)	With cardiovascular disease (N=6436), n (%)	Without cardiovascular disease (N=14253), n (%)	P- value
Age, in years				<.0001
Mean (\pm STD)	69.5 (\pm 11)	73.7 (\pm 9.7)	67.6 (\pm 11.1)	
Median (IQR)	70 (62 - 78)	75 (67 - 81)	68 (60 - 76)	
Age group				<.0001
<=60	4443 (21.5 %)	658 (10.2 %)	3785 (26.6 %)	
61-70	6112 (29.5 %)	1549 (24.1 %)	4563 (32 %)	
71-80	6717 (32.5 %)	2590 (40.2 %)	4127 (29 %)	
>80	3417 (16.5 %)	1639 (25.5 %)	1778 (12.5 %)	
Sex				<.0001
Female	10156 (49.1 %)	2874 (44.7 %)	7282 (51.1 %)	
Male	10533 (50.9 %)	3562 (55.3 %)	6971 (48.9 %)	
Year of diagnosis				0.0337
2004-2009	9993 (48.3 %)	3038 (47.2 %)	6955 (48.8 %)	
2010-2015	10696 (51.7 %)	3398 (52.8 %)	7298 (51.2 %)	
CCI score				<.0001
0	2566 (12.4 %)	310 (4.8 %)	2256 (15.8 %)	
1	2614 (12.6 %)	627 (9.7 %)	1987 (13.9 %)	
>1	15509 (75 %)	5499 (85.4 %)	10010 (70.2 %)	
Histology				<.0001

Adenocarcinoma	7727 (37.3 %)	2024 (31.4 %)	5703 (40 %)	
SCC	3680 (17.8 %)	1184 (18.4 %)	2496 (17.5 %)	
SCLC	2571 (12.4 %)	799 (12.4 %)	1772 (12.4 %)	
Carcinoid/LCNE	520 (2.5 %)	117 (1.8 %)	403 (2.8 %)	
Large cell cancer	260 (1.3 %)	59 (0.9 %)	201 (1.4 %)	
Others	5931 (28.7 %)	2253 (35 %)	3678 (25.8 %)	
Stage				
I	3636 (17.6 %)	1127 (17.5 %)	2509 (17.6 %)	<.0001
II	880 (4.3 %)	250 (3.9 %)	630 (4.4 %)	
III	5168 (25 %)	1591 (24.7 %)	3577 (25.1 %)	
IV	10409 (50.3 %)	3207 (49.8 %)	7202 (50.5 %)	
Unknown	596 (2.9 %)	261 (4.1 %)	335 (2.4 %)	
T stage				
T0	110 (0.5 %)	44 (0.7 %)	66 (0.5 %)	<.0001
T1	3095 (15 %)	985 (15.3 %)	2110 (14.8 %)	
T2	6581 (31.8 %)	2001 (31.1 %)	4580 (32.1 %)	
T3	788 (3.8 %)	188 (2.9 %)	600 (4.2 %)	
T4	9378 (45.3 %)	2966 (46.1 %)	6412 (45 %)	
Unknown	737 (3.6 %)	252 (3.9 %)	485 (3.4 %)	
N stage				
N0	6540 (31.6 %)	2126 (33 %)	4414 (31 %)	<.0001

	%)			
N1	1729 (8.4 %)	494 (7.7 %)	1235 (8.7 %)	
N2	7453 (36 %)	2302 (35.8 %)	5151 (36.1 %)	
N3	3803 (18.4 %)	1073 (16.7 %)	2730 (19.2 %)	
Unknown	1164 (5.6 %)	441 (6.9 %)	723 (5.1 %)	
M stage				
M0	9877 (47.7 %)	3069 (47.7 %)	6808 (47.8 %)	0.0008
M1	10409 (50.3 %)	3207 (49.8 %)	7202 (50.5 %)	
Unknown	403 (1.9 %)	160 (2.5 %)	243 (1.7 %)	
Laterality				
Bilateral	211 (1 %)	74 (1.1 %)	137 (1 %)	0.0003
Left	8477 (41 %)	2677 (41.6 %)	5800 (40.7 %)	
Right	11568 (55.9 %)	3515 (54.6 %)	8053 (56.5 %)	
Unknown	433 (2.1 %)	170 (2.6 %)	263 (1.8 %)	
Surgery				
No	17274 (83.5 %)	5721 (88.9 %)	11553 (81.1 %)	<.0001
Lobectomy or segmental	3168 (15.3 %)	686 (10.7 %)	2482 (17.4 %)	
Pneumonectomy	247 (1.2 %)	29 (0.5 %)	218 (1.5 %)	
Chemotherapy				
No	15029 (72.6 %)	5378 (83.6 %)	9651 (67.7 %)	<.0001
Yes	5660 (27.4 %)	1058 (16.4 %)	4602 (32.3 %)	
Immunotherapy				

No	20669 (99.9 %)	6433 (100 %)	14236 (99.9 %)	0.1195
Yes	20 (0.1 %)	3 (0 %)	17 (0.1 %)	
Radiation				
No	14418 (69.7 %)	4743 (73.7 %)	9675 (67.9 %)	<.0001
Yes	6271 (30.3 %)	1693 (26.3 %)	4578 (32.1 %)	
Institution type				
Academic	10713 (51.8 %)	3119 (48.5 %)	7594 (53.3 %)	<.0001
Community	9976 (48.2 %)	3317 (51.5 %)	6659 (46.7 %)	
Driving time (hours)				
1	15419 (74.5 %)	4704 (73.1 %)	10715 (75.2 %)	<.0001
2	2885 (13.9 %)	1010 (15.7 %)	1875 (13.2 %)	
>2	2385 (11.5 %)	722 (11.2 %)	1663 (11.7 %)	
Health Zone				
Calgary	6192 (29.9 %)	1781 (27.7 %)	4411 (30.9 %)	<.0001
Central	3125 (15.1 %)	1045 (16.2 %)	2080 (14.6 %)	
Edmonton	7159 (34.6 %)	2239 (34.8 %)	4920 (34.5 %)	
North	2459 (11.9 %)	755 (11.7 %)	1704 (12 %)	
South	1754 (8.5 %)	616 (9.6 %)	1138 (8 %)	
Educational level*				
<= 80%	10133 (49 %)	3281 (51 %)	6852 (48.1 %)	0.0005
> 80%	10527 (50.9 %)	3147 (48.9 %)	7380 (51.8 %)	

Unknown	29 (0.1 %)	8 (0.1 %)	21 (0.1 %)	
Income level				
<= 46k	12849 (62.1 %)	4085 (63.5 %)	8764 (61.5 %)	0.0237
> 46k	7811 (37.8 %)	2343 (36.4 %)	5468 (38.4 %)	
Unknown	29 (0.1 %)	8 (0.1 %)	21 (0.1 %)	
cardiovascular disease: cardiovascular disease. *80% of residents have high school and above level of education in the neighborhood.				

Pre-existing cardiovascular diseases

Of all patients with lung cancer, 6436 (31.1%) had at least one pre-existing cardiovascular disease. The most common pre-existing cardiovascular disease at the diagnosis of lung cancer included congestive heart failure (47.4%), followed by previous cerebrovascular accident (40.3%), myocardial infarction (33.0%), and chronic arrhythmias (30.4%), respectively (Table 2).

Table 2
Type of cardiovascular disease

Cardiovascular disease	Number (percentage of those with cardiovascular disease) (n = 6436)	Percentage of overall population (n = 20689)
Previous myocardial infarction	2127 (33%)	10.3%
Congestive heart failure	3049 (47.4%)	14.7%
Cerebrovascular accident	2596 (40.3%)	12.5%
Chronic arrhythmias	1954 (30.4%)	9.4%

Patients with pre-existing cardiovascular disease were more likely to be older (mean age 73.7 vs. 67.6 years, $P < 0.0001$), male (55.3% vs. 48.9%, $P < 0.0001$), have a higher burden of comorbid conditions (Charlson's comorbidity index score > 1 , 85.4% vs. 70.2%, $P < 0.0001$), and advanced stages of lung cancer at diagnosis (stage III and IV, 74.5% vs. 75.6%, $P < 0.0001$). Similarly, they were more likely to have lower neighborhood-level income ($< 46K$ per year, 36.4% vs. 38.4%, $P = 0.0237$) and education levels ($> 80\%$ population attained high-school or greater, 48.9% vs. 51.8%, $P = 0.0005$), and also tended to reside rurally (37.5% vs. 34.6%, $P < 0.0001$). The driving time from place of residence to cancer center (> 2 hours, 11.2% vs 11.7%, $P < 0.0001$) was also longer in this subpopulation.

Patients with lung cancer and pre-existing cardiovascular disease were less likely to be treated with surgery (11.2% vs. 18.9%, $P < 0.0001$), chemotherapy (16.4% vs. 32.3%, $P < 0.0001$), or radiotherapy (26.3% vs. 32.1%, $P < 0.0001$). Moreover, such patients were more likely to be treated in community centers rather than academic institutions (51.5% vs. 46.7%, $P < 0.0001$).

Pre-existing cardiovascular disease and treatment patterns

We used multivariable logistic regression analysis to assess the impact of pre-existing cardiovascular disease on lung cancer treatment, including chemotherapy, radiation therapy, and surgery (Table 3). Adjusting for baseline variables including age, sex, year of diagnosis, Charlson's comorbidity index, histological subtype, stage (T, N, and M), laterality, other treatments, management at either academic or community center, zone of residence, driving distance from residence to nearest cancer center, education and income levels, the presence of pre-existing cardiovascular disease was associated with lower likelihood of chemotherapy (odds ratio, 0.53; 95% confidence interval [CI], 0.48 to 0.58; $P < 0.0001$), radiation therapy (odds ratio, 0.76; 95% CI 0.7 to 0.82, $P < 0.0001$) or surgery (odds ratio, 0.56; 95% CI, 0.44 to 0.7; $P < 0.0001$), respectively.

Table 3

Multivariable Logistic regression for factors associated with surgery, chemotherapy, and radiation therapy in patients with lung cancer

Variable	Chemotherapy		Radiation		Surgery	
	Odds Ratio (95% Confidence Limit)	P value	Odds Ratio (95% Confidence Limit)	P value	Odds Ratio (95% Confidence Limit)	P value
Age group						
<=60	Reference		Reference		Reference	
61–70	0.68 (0.62 to 0.75)	< .0001	0.82 (0.74 to 0.9)	< .0001	0.57 (0.44 to 0.75)	< .0001
71–80	0.34 (0.3 to 0.37)	< .0001	0.61 (0.55 to 0.67)	< .0001	0.35 (0.27 to 0.46)	< .0001
> 80	0.09 (0.08 to 0.11)	< .0001	0.38 (0.34 to 0.43)	< .0001	0.12 (0.08 to 0.18)	< .0001
Sex						
Female	Reference		Reference		Reference	
Male	0.92 (0.85 to 0.99)	0.0225	1.11 (1.04 to 1.18)	0.0029	0.99 (0.82 to 1.21)	0.9448
Year of diagnosis	1.01 (1 to 1.02)	0.0337	1 (0.99 to 1.01)	0.6327	0.99 (0.96 to 1.02)	0.4833
CCI score						
0	Reference		Reference		Reference	
1	0.77 (0.67 to 0.89)	0.0002	1.02 (0.89 to 1.17)	0.7471	0.79 (0.55 to 1.13)	0.1945
> 1	0.68 (0.61 to 0.75)	< .0001	1.16 (1.04 to 1.29)	0.0058	0.68 (0.52 to 0.9)	0.0078
cardiovascular disease						
No	Reference		Reference		Reference	
Yes	0.53 (0.48 to 0.58)	< .0001	0.76 (0.7 to 0.82)	< .0001	0.56 (0.44 to 0.7)	< .0001
Histology						
Adenocarcinoma	Reference		Reference		Reference	

cardiovascular disease: cardiovascular disease. *80% of residents have high school and above level of education in the neighborhood.

Variable	Chemotherapy		Radiation		Surgery	
	Odds Ratio (95% Confidence Limit)	P value	Odds Ratio (95% Confidence Limit)	P value	Odds Ratio (95% Confidence Limit)	P value
SCC	0.61 (0.55 to 0.68)	< .0001	0.77 (0.71 to 0.85)	< .0001	0.12 (0.08 to 0.16)	< .0001
SCLC	6.64 (5.93 to 7.45)	< .0001	2.17 (1.96 to 2.39)	< .0001	0.47 (0.37 to 0.61)	< .0001
Carcinoid/LCNE	1.05 (0.84 to 1.31)	0.6779	0.82 (0.62 to 1.08)	0.148	3.46 (2.16 to 5.54)	< .0001
Large cell ca	0.79 (0.58 to 1.08)	0.1382	1.98 (1.45 to 2.71)	< .0001	9.65 (4.74 to 19.6)	< .0001
Others	6.64 (5.93 to 7.45)	< .0001	0.71 (0.63 to 0.79)	< .0001	0.48 (0.32 to 0.73)	0.0005
T stage						
T0	Reference		Reference			
T1	0.63 (0.37 to 1.09)	0.1007	1.39 (0.78 to 2.48)	0.2709	Reference	
T2	1.02 (0.59 to 1.75)	0.9435	1.74 (0.98 to 3.09)	0.0588	0.78 (0.61 to 1)	0.0517
T3	1.28 (0.73 to 2.24)	0.391	3.52 (1.94 to 6.39)	< .0001	0.75 (0.48 to 1.17)	0.204
T4	1 (0.58 to 1.7)	0.9861	1.65 (0.93 to 2.93)	0.0862	0.2 (0.15 to 0.27)	< .0001
Unknown	0.74 (0.42 to 1.29)	0.2909	1.06 (0.58 to 1.92)	0.8544	0.97 (0.46 to 2.03)	0.9319
N stage						
N0	Reference		Reference		Reference	
N1	2.72 (2.37 to 3.12)	< .0001	1.07 (0.93 to 1.24)	0.34	0.97 (0.72 to 1.3)	0.8284
N2	2.22 (1.99 to 2.48)	< .0001	1.66 (1.51 to 1.82)	< .0001	0.13 (0.1 to 0.17)	< .0001
N3	2.36 (2.08 to 2.67)	< .0001	1.73 (1.55 to 1.92)	< .0001	0.02 (0.01 to 0.03)	< .0001

cardiovascular disease: cardiovascular disease. *80% of residents have high school and above level of education in the neighborhood.

Variable	Chemotherapy		Radiation		Surgery	
	Odds Ratio (95% Confidence Limit)	P value	Odds Ratio (95% Confidence Limit)	P value	Odds Ratio (95% Confidence Limit)	P value
Unknown	1.05 (0.84 to 1.32)	0.6623	0.68 (0.56 to 0.82)	< .0001	0.28 (0.15 to 0.51)	< .0001
M stage						
M0	Reference		Reference		Reference	
M1	0.65 (0.6 to 0.71)	< .0001	0.35 (0.32 to 0.37)	< .0001	0.03 (0.02 to 0.04)	< .0001
Unknown	0.29 (0.18 to 0.45)	< .0001	0.28 (0.2 to 0.39)	< .0001	1.34 (0.61 to 2.92)	0.4665
Laterality						
Bilateral	Reference		Reference		Reference	
Left	0.62 (0.43 to 0.88)	0.0071	3.46 (2.13 to 5.63)	< .0001	5.62 (0.69 to 45.6)	0.1063
Right	0.56 (0.39 to 0.79)	0.0012	3.59 (2.21 to 5.83)	< .0001	5.63 (0.69 to 45.6)	0.1058
Unknown	0.47 (0.3 to 0.74)	0.0012	1.82 (1.03 to 3.22)	0.0397		
Chemotherapy						
0			Reference		Reference	
1			1.21 (1.11 to 1.31)	< .0001	1.85 (1.45 to 2.35)	< .0001
Surgery type						
Segmental	Reference		Reference			
Non-surgery	1.32 (1.13 to 1.55)	0.0006	36.5(29.3 to 45.48)	< .0001		
Pneumonectomy	1.8 (1.34 to 2.41)	< .0001	0.43 (0.2 to 0.95)	0.0363		
Radiation						
0	Reference				Reference	

cardiovascular disease: cardiovascular disease. *80% of residents have high school and above level of education in the neighborhood.

Variable	Chemotherapy		Radiation		Surgery	
	Odds Ratio (95% Confidence Limit)	P value	Odds Ratio (95% Confidence Limit)	P value	Odds Ratio (95% Confidence Limit)	P value
1	1.18 (1.08 to 1.28)	0.0001			0.05 (0.04 to 0.07)	< .0001
Immunotherapy						
0	Reference		Reference		Reference	
1	4.06 (1.53 to 10.8)	0.005	0.79 (0.29 to 2.1)	0.6303	0.02 (0 to 0.31)	0.0045
Institution type						
Academic	Reference		Reference		Reference	
Community	0.81 (0.74 to 0.89)	< .0001	0.9 (0.83 to 0.98)	0.0097	0 (0 to 0.01)	< .0001
Driving time (hours)						
1	Reference		Reference		Reference	
2	0.88 (0.77 to 1)	0.0563	0.97 (0.86 to 1.1)	0.6531	1.93 (1.17 to 3.19)	0.0097
> 2	0.92 (0.75 to 1.12)	0.4131	0.9 (0.74 to 1.08)	0.2578	1.05 (0.53 to 2.08)	0.8908
Health Zone						
Calgary	Reference		Reference		Reference	
Central	1.36 (1.19 to 1.56)	< .0001	0.75 (0.66 to 0.85)	< .0001	5.21 (3.26 to 8.34)	< .0001
Edmonton	0.97 (0.89 to 1.06)	0.5263	0.99 (0.91 to 1.08)	0.8189	1.9 (1.52 to 2.36)	< .0001
North	1.17 (0.95 to 1.44)	0.1448	0.94 (0.77 to 1.15)	0.5443	6.86 (3.4 to 13.85)	< .0001
South	1.29 (1.1 to 1.52)	0.0019	0.92 (0.79 to 1.06)	0.2432	2.66 (1.38 to 5.16)	0.0036
Education level*						
<= 80%	Reference		Reference		Reference	

cardiovascular disease: cardiovascular disease. *80% of residents have high school and above level of education in the neighborhood.

Variable	Chemotherapy		Radiation		Surgery	
	Odds Ratio (95% Confidence Limit)	P value	Odds Ratio (95% Confidence Limit)	P value	Odds Ratio (95% Confidence Limit)	P value
> 80%	1.06 (0.98 to 1.15)	0.1557	1 (0.92 to 1.08)	0.948	0.94 (0.75 to 1.18)	0.6046
Income level						
<= 46 k	Reference		Reference		Reference	
> 46 k	1.21 (1.12 to 1.32)	< .0001	1.03 (0.95 to 1.11)	0.4565	1.35 (1.09 to 1.67)	0.0069
cardiovascular disease: cardiovascular disease. *80% of residents have high school and above level of education in the neighborhood.						

Impact of pre-existing cardiovascular disease on survival outcomes

The median overall survival (OS) of patients with lung cancer and pre-existing cardiovascular disease was significantly shorter (13.5 [95% CI, 12.8–14.2] years) compared with those without any baseline cardiovascular disease (23.5 [95% CI, 22.8–24.2] years, $P < 0.0001$) (Fig. 1). Likewise, cancer specific survival (CSS) was significantly shorter for those with pre-existing cardiovascular disease (15.2 vs 24.8 years, $P < 0.0001$).

Multivariable Cox regression model was constructed to analyze the factors that impacted OS and CSS (Table 4). Adjusting for baseline factors, pre-existing cardiovascular disease was predictive of inferior OS (hazard ratio, 1.1; 95% CI, 1.1 to 1.2; $P < 0.0001$), as well as shorter CSS (hazard ratio, 1.1; 95% CI, 1.1 to 1.1; $P < 0.0001$), respectively. Other factors predictive of shorter OS and CSS included older age, male sex, Charlson's comorbidity index > 1 , histologies other than carcinoid and adenocarcinoma, advanced TNM stage, and > 2 hours drive from residence to the nearest cancer center. Conversely, treatment with surgery, chemotherapy, or radiotherapy predicted longer OS and CSS. Notably, treatment setting (academic vs community treatment center), education, and income did not influence survival outcomes.

Table 4

Multivariable Cox regression model for factors associated with overall survival and cancer-specific survival in patients with lung cancer

Variable	Overall survival		Cancer specific survival	
	Hazard Ratio (95% Confidence Limit)	P value	Hazard Ratio (95% Confidence Limit)	P value
Age group				
<=60	Reference		Reference	
61–70	1.1 (1 to 1.1)	0.0005	1.1 (1 to 1.1)	0.0061
71–80	1.1 (1 to 1.1)	0.0012	1 (1 to 1.1)	0.2039
> 80	1.1 (1.1 to 1.2)	< .0001	1.1 (1 to 1.1)	0.0037
Sex				
Female	Reference		Reference	
Male	1.2 (1.2 to 1.2)	< .0001	1.2 (1.2 to 1.2)	< .0001
Year of diagnosis	1 (1 to 1)	0.0012	1 (1 to 1)	0.1635
CCI score				
0	Reference		Reference	
1	1 (0.9 to 1)	0.2999	1 (0.9 to 1)	0.145
> 1	1.2 (1.1 to 1.2)	< .0001	1.2 (1.1 to 1.2)	< .0001
cardiovascular disease				
Yes	Reference		Reference	
No	1.1 (1.1 to 1.2)	< .0001	1.1 (1.1 to 1.1)	< .0001
Histology				
Adenocarcinoma	Reference		Reference	
SCC	1.1 (1 to 1.1)	0.0182	1 (1 to 1.1)	0.2506
SCLC	1.6 (1.5 to 1.7)	< .0001	1.6 (1.5 to 1.7)	< .0001
Carcinoid/LCNE	0.7 (0.7 to 0.8)	< .0001	0.8 (0.7 to 0.9)	< .0001
Large cell ca	1.3 (1.1 to 1.4)	0.0011	1.3 (1.1 to 1.5)	0.0005
Others	1.2 (1.2 to 1.3)	< .0001	1.2 (1.2 to 1.3)	< .0001
cardiovascular disease: cardiovascular disease. *80% of residents have high school and above level of education in the neighborhood.				

Variable	Overall survival		Cancer specific survival	
	Hazard Ratio (95% Confidence Limit)	P value	Hazard Ratio (95% Confidence Limit)	P value
T stage				
T0	Reference		Reference	
T1	1.3 (1 to 1.6)	0.0394	1.1 (0.9 to 1.4)	0.2457
T2	1.8 (1.5 to 2.3)	< .0001	1.8 (1.4 to 2.2)	< .0001
T3	2.5 (2 to 3.1)	< .0001	2.4 (1.9 to 3)	< .0001
T4	2.6 (2.1 to 3.2)	< .0001	2.5 (2 to 3.1)	< .0001
Unknown	1.8 (1.4 to 2.2)	< .0001	1.7 (1.4 to 2.2)	< .0001
N stage				
N0	Reference		Reference	
N1	1.4 (1.3 to 1.5)	< .0001	1.5 (1.4 to 1.6)	< .0001
N2	1.8 (1.7 to 1.8)	< .0001	1.9 (1.8 to 1.9)	< .0001
N3	1.8 (1.7 to 1.9)	< .0001	1.9 (1.8 to 2)	< .0001
Unknown	1.6 (1.5 to 1.7)	< .0001	1.7 (1.5 to 1.8)	< .0001
M stage				
M0	Reference		Reference	
M1	1.9 (1.8 to 1.9)	< .0001	2 (1.9 to 2.1)	< .0001
Unknown	0.9 (0.8 to 1)	0.2007	0.9 (0.8 to 1.1)	0.2776
Lateral				
Bilateral	Reference		Reference	
Left	1.3 (1.1 to 1.5)	0.0001	1.3 (1.1 to 1.5)	0.0014
Right	1.3 (1.2 to 1.5)	< .0001	1.3 (1.1 to 1.5)	0.0005
Unknown	2 (1.7 to 2.4)	< .0001	1.9 (1.6 to 2.3)	< .0001
Surgery type				
Pneumonectomy	Reference		Reference	

cardiovascular disease: cardiovascular disease. *80% of residents have high school and above level of education in the neighborhood.

Variable	Overall survival		Cancer specific survival	
	Hazard Ratio (95% Confidence Limit)	P value	Hazard Ratio (95% Confidence Limit)	P value
Lobectomy or segmental	0.7 (0.6 to 0.9)	0.0002	0.6 (0.5 to 0.8)	< .0001
Non-surgery	2.8 (2.4 to 3.3)	< .0001	2.7 (2.3 to 3.3)	< .0001
Chemotherapy				
No	Reference		Reference	
Yes	0.4 (0.4 to 0.4)	< .0001	0.4 (0.4 to 0.4)	< .0001
Radiation				
No	Reference		Reference	
Yes	0.6 (0.6 to 0.7)	< .0001	0.6 (0.6 to 0.7)	< .0001
Surgery institution type				
Academic	Reference		Reference	
Community	1 (1 to 1.1)	0.44	1 (1 to 1.1)	0.069
Driving time (hours)				
1	Reference		Reference	
2	1 (1 to 1.1)	0.5613	1 (1 to 1.1)	0.4693
3	0.9 (0.8 to 1)	0.0215	0.9 (0.8 to 1)	0.0073
Zone name				
Calgary	Reference		Reference	
Central	1.1 (1 to 1.1)	0.004	1.1 (1 to 1.1)	0.03
Edmonton	1.1 (1 to 1.1)	< .0001	1.1 (1.1 to 1.1)	< .0001
North	1.2 (1.1 to 1.3)	< .0001	1.2 (1.1 to 1.3)	< .0001
South	1.2 (1.1 to 1.3)	< .0001	1.2 (1.1 to 1.3)	< .0001
Education level				
<= 80%	Reference		Reference	

cardiovascular disease: cardiovascular disease. *80% of residents have high school and above level of education in the neighborhood.

Variable	Overall survival		Cancer specific survival	
	Hazard Ratio (95% Confidence Limit)	P value	Hazard Ratio (95% Confidence Limit)	P value
> 80%	1 (1 to 1)	0.3769	1 (1 to 1)	0.5999
Income level				
<= 46 k	Reference		Reference	
> 46 k	1 (1 to 1)	0.9992	1 (1 to 1)	0.8051
cardiovascular disease: cardiovascular disease. *80% of residents have high school and above level of education in the neighborhood.				

The presence of pre-existing cardiovascular disease can alter the effect of various treatments on the outcomes of patients with lung cancer. Therefore, we assessed for any effect modification by examining interactions in the statistical models. The effect of baseline cardiovascular disease on OS varied for chemotherapy (P = 0.026), surgery (P < .0001), and radiotherapy (P = 0.001). Likewise for CSS, the interactions were significant for radiotherapy and surgery (P = 0.05, and P = 0.001, respectively). However, the interaction of chemotherapy on CSS showed only a trend towards significance (P = 0.06).

Discussion

In this large study of over 20,000 patients that included patients across all stages of lung cancer, approximately one-third of patients had pre-existing cardiovascular disease, most commonly congestive heart failure. The presence of baseline heart disease was associated with a lower likelihood of receiving any form of cancer treatment including chemotherapy, radiotherapy or surgery. Further, pre-existing cardiovascular disease in patients with lung cancer predicted for inferior survival outcomes, including OS and CSS.

A previous study from the United States linking the Surveillance, Epidemiology, and End Results data and Medicare (SEER) data reported on the effect of cardiovascular disease on survival outcomes in patients with non-small cell lung cancer. Ischemic heart disease (33.7%), cardiac arrhythmias (28.6%), and congestive heart failure (17.5%) were the common cardiovascular diseases reported in that study(23). The corresponding prevalence of these conditions in our study were lower at 10.3%, 9.4%, and 14.7%, respectively. One potential reason for this difference is that the age group of patients across studies were remarkably different. While older age was not an exclusion criterion and 21.5% of patients were less than 60 years old in the current study, those less than 65 years were excluded from the study in the United States. Moreover, a lower frequency of obesity and cigarette smoking in Canadians as compared with Americans may be another factor contributing to the observed differences in cardiovascular diseases(26, 27).

The prevalence of baseline cardiovascular disease in patients with breast cancer was as low as 8% in a prior Canadian study(21). However, that study included women exclusively and the median age of patients was 59 years. The higher prevalence of cardiovascular disease in this study may reflect the larger proportion of older males in the current study cohort (28). Notably, the pattern of cardiovascular diseases was also different. For instance, cerebrovascular accidents (2.6%) and cardiac arrhythmias (2.0%) were more common than heart failure (1.8%) and myocardial infarction (1.1%) in women with breast cancer. Conversely, heart failure (14.7%) and cerebrovascular accidents (12.5%) were more prevalent than myocardial infarction (10.3%) and cardiac arrhythmias (9.4%) in patients with lung cancer. The drivers of these differences are likely multifactorial, but one factor could be the role of estrogen in preventing ischemic heart disease in younger women. Another reason could be differences in modifiable risk factors, such as smoking and obesity, between men and women (28, 29).

As expected, patients with baseline cardiovascular disease were less likely to receive any form of treatment for lung cancer. It is likely that a proportion of these patients were considered unfit to receive therapy, in which case their lack of treatment is clinically appropriate. However, we hypothesized that others may have been denied treatment because of perceived concerns that their cardiovascular comorbidity may place them at heightened risk of toxicities or because of the absence of data from clinical trials regarding the safety of chemotherapy administration in patients with heart disease (30). (31). It has been reported that heart disease represents the second most common cause of ineligibility for clinical trials. This results in limited data to guide oncologists when they treat comorbid patients in the real-world and contributes to variations in management whereby physicians based their decisions on anecdotal experience. It is likely in these scenarios that physicians resort to the use of patient-related factors such as age and performance status, as well as the expertise of cardio-oncologists in formulating their treatment plans(32, 33). Broadening of eligibility criteria in clinical trials to represent patients with a history of cardiovascular disease will increase the generalizability of results to real-world patients and optimize evidence-based treatment in this subpopulation.

Our study found that the OS and CSS of patients with lung cancer who had baseline cardiovascular disease were worse compared to those without pre-existing cardiac comorbid conditions. Similar findings were reported in the SEER and Medicare linked study from the United States of older beneficiaries (23). Another small study of 247 patients with limited stage lung cancer also showed increased postoperative morbidity and mortality among patients with lung cancer and pre-existing cardiovascular disease(22). Importantly, inferior OS and CSS were also reported in a large Canadian study of patients with breast cancer and baseline cardiovascular disease, suggesting that this observation may persist across different tumor types(21).

The management of lung cancer is experiencing a significant paradigm shift with the recent approvals of various targeted therapies and immune checkpoint inhibitors, all of which have demonstrated improved survival across different subsets of patients with lung cancer(34–38). In this study, patients with pre-existing cardiovascular disease were less likely to receive immunotherapy, although only 20 patients received checkpoint inhibitors in our cohort. The use of novel immunotherapeutic agents in patients with

lung cancer is increasing after they were approved in Canada in 2016(39, 40). Since one-third of patients with lung cancer were found to have associated cardiovascular disease, it is imperative that early cardio-oncology consultations be sought in such patients to optimize the concurrent management of comorbid conditions so that the benefit of novel therapies can be extended to these patients in the real-world.

The study was limited by its retrospective design and use of administrative sources for data. Therefore, the clinical severity of cardiovascular disease and performance status could not be ascertained reliably. Second, the presence of cardiovascular disease was assumed as the reason for not receiving treatment, even though additional factors such as patient preference and physician discretion are major contributors to treatment decisions. However, the large sample size of our study and the population-based nature of the data are major strengths.

Conclusions

In summary, a significant proportion of patients with lung cancer have baseline cardiovascular disease, which is associated with a lower likelihood of receiving any cancer treatment and also with worse survival outcomes. With a plethora of novel therapies being developed, early engagement and co-management with experts in cardio-oncology can help to optimize the number of lung cancer patients who can derive benefit from emerging therapies.

Abbreviations

ACR

Alberta Cancer Registry

ICD-10

International Classification of Diseases tenth version

OS

Overall Survival

CSS

Cancer Specific Survival

CI

Confidence Interval

OR

Odds Ratio

HR

Hazard Ratio

Declarations

Ethics approval and consent to participate

Approval was obtained from the Health Research Ethics Board of Alberta's Cancer Committee prior to commencing this study. The need for consent from individual patient was waived.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests" in this section.

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Authors' contributions

Atul Batra: Conceptualization, data collection and analysis, writing- original draft, editing DropenSheka: Data collection, writing Shiyong Kong: Data collection and analysis Winson Cheung: Conceptualization, data collection and analysis, writing-reviewing and editing, editing, supervision

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References

1. Cardiovascular diseases [Internet]. [cited 2020 Mar 21]. Available from: <https://www.who.int/westernpacific/health-topics/cardiovascular-diseases>.
2. Cancer [Internet]. [cited 2020 Mar 11]. Available from: <https://www.who.int/news-room/fact-sheets/detail/cancer>.

3. GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017 Sep 16;390(10100):1151–210.
4. Dawber TR, Kannel WB, Revotskie N, Stokes J, Kagan A, Gordon T. Some factors associated with the development of coronary heart disease: six years' follow-up experience in the Framingham study. *Am J Public Health Nations Health*. 1959 Oct;49:1349–56.
5. Masoudkibir F, Sarrafzadegan N, Gotay C, Ignaszewski A, Krahn AD, Davis MK, et al. Cardiovascular disease and cancer: Evidence for shared disease pathways and pharmacologic prevention. *Atherosclerosis*. 2017;263:343–51.
6. Ligibel JA, Alfano CM, Courneya KS, Demark-Wahnefried W, Burger RA, Chlebowski RT, et al. American Society of Clinical Oncology position statement on obesity and cancer. *J Clin Oncol*. 2014 Nov 1;32(31):3568–74.
7. Tourmousoglou CE, Apostolakis E, Dougenis D. Simultaneous occurrence of coronary artery disease and lung cancer: what is the best surgical treatment strategy? *Interact Cardiovasc Thorac Surg*. 2014 Oct;19(4):673–81.
8. Kreatsoulas C, Anand SS, Subramanian SV. An emerging double burden of disease: the prevalence of individuals with cardiovascular disease and cancer. *J Intern Med*. 2014 May;275(5):494–505.
9. Inohara T, Endo A, Melloni C. Unmet Needs in Managing Myocardial Infarction in Patients With Malignancy. *Front Cardiovasc Med* [Internet]. 2019 May 17 [cited 2020 Mar 21];6. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6533845/>.
10. Blaes AH, Shenoy C. Is it time to include cancer in cardiovascular risk prediction tools? *The Lancet*. 2019 Sep 21;394(10203):986–8.
11. Alberg AJ, Samet JM. Epidemiology of lung cancer. *Chest*. 2003 Jan;123(1 Suppl):21S–49S.
12. Kamp DW, Shacter E, Weitzman SA. Chronic inflammation and cancer: the role of the mitochondria. *Oncology (Williston Park, NY)*. 2011 Apr 30;25(5):400–10, 413.
13. Barrera G. Oxidative stress and lipid peroxidation products in cancer progression and therapy. *ISRN Oncol*. 2012;2012:137289.
14. Tesfamariam B, Cohen RA. Free radicals mediate endothelial cell dysfunction caused by elevated glucose. *Am J Physiol*. 1992 Aug;263(2 Pt 2):H321–6.
15. Cancer of the Lung and Bronchus. - Cancer Stat Facts [Internet]. SEER. [cited 2019 Nov 19]. Available from: <https://seer.cancer.gov/statfacts/html/lungb.html>.
16. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, et al. Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2009 Jan 27;119(3):e21-181.
17. Vyskočil J, Petráková K, Jelínek P, Furdek M. [Cardiovascular complications of cancers and anti-cancer therapy]. *Vnitr Lek*. 2017 Spring;63(3):200–9.

18. Daher IN, Daigle TR, Bhatia N, Durand J-B. The Prevention of Cardiovascular Disease in Cancer Survivors. *Tex Heart Inst J*. 2012;39(2):190–8.
19. Al-Kindi SG, Oliveira GH. Prevalence of Preexisting Cardiovascular Disease in Patients With Different Types of Cancer: The Unmet Need for Onco-Cardiology. *Mayo Clin Proc*. 2016 Jan;91(1):81–3.
20. Liu D, Ma Z, Yang J, Zhao M, Ao H, Zheng X, et al. Prevalence and prognosis significance of cardiovascular disease in cancer patients: a population-based study. *Aging*. 2019 Sep;27(18):7948–60. 11(.
21. Abdel-Rahman O, Xu Y, Kong S, Dort J, Quan ML, Karim S, et al. Impact of Baseline Cardiovascular Comorbidity on Outcomes in Women With Breast Cancer: A Real-world, Population-based Study. *Clin Breast Cancer*. 2019;19(2):e297–305.
22. Ambrogi V, Pompeo E, Elia S, Pistolese GR, Mineo TC. The impact of cardiovascular comorbidity on the outcome of surgery for stage I and II non-small-cell lung cancer. *Eur J Cardiothorac Surg*. 2003 May 1;23(5):811–7.
23. Kravchenko J, Berry M, Arbeev K, Lysterly HK, Yashin A, Akushevich I. Cardiovascular comorbidities and survival of lung cancer patients: Medicare data based analysis. *Lung Cancer*. 2015 Apr;88(1):85–93.
24. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi J-C, et al. Coding Algorithms for Defining Comorbidities in ICD-9-CM and ICD-10 Administrative Data. *Med Care*. 2005 Nov;43(11):1130–9.
25. Ambroggi M, Biasini C, Del Giovane C, Fornari F, Cavanna L. Distance as a Barrier to Cancer Diagnosis and Treatment: Review of the Literature. *Oncologist*. 2015 Dec;20(12):1378–85.
26. Jones A, Gulbis A, Baker EH. Differences in tobacco use between Canada and the United States. *Int J Public Health*. 2010 Jun;55(3):167–75.
27. Shields M, Carroll MD, Ogden CL. Adult obesity prevalence in Canada and the United States. *NCHS Data Brief*. 2011 Mar;(56):1–8.
28. Robitaille C, McRae L, Toews J. MONITORING THE BURDEN OF HEART DISEASE WITH THE CANADIAN CHRONIC DISEASE SURVEILLANCE SYSTEM. *Canadian Journal of Cardiology*. 2017 Oct 1;33(10):S138–9.
29. Möller-Leimkühler AM. Gender differences in cardiovascular disease and comorbid depression. *Dialogues Clin Neurosci*. 2007 Mar;9(1):71–83.
30. Booton R, Jones M, Thatcher N. Lung cancer • 7: Management of lung cancer in elderly patients. *Thorax*. 2003 Aug 1;58(8):711–20.
31. Karim S, Xu Y, Kong S, Abdel-Rahman O, Quan ML, Cheung WY. Generalisability of Common Oncology Clinical Trial Eligibility Criteria in the Real World. *Clinical Oncology*. 2019 Sep 1;31(9):e160–6.
32. Coviello JS. Cardiovascular and Cancer Risk: The Role of Cardio-oncology. *J Adv Pract Oncol*. 2018 Mar;9(2):160–76.
33. Fradley MG, Brown AC, Shields B, Viganego F, Damrongwatanasuk R, Patel AA, et al. Developing a Comprehensive Cardio-Oncology Program at a Cancer Institute: The Moffitt Cancer Center

- Experience. *Oncol Rev* [Internet]. 2017 Jul 18 [cited 2020 Mar 25];11(2). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5523022/>.
34. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csósz T, Fülöp A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *N Engl J Med*. 2016;10(19):1823–33. 375(.
 35. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim D-W, et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. *N Engl J Med*. 2017;31(9):829–38. 377(.
 36. Soria J-C, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. *N Engl J Med*. 2018;11(2):113–25. 378(.
 37. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümüş M, Mazières J, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. *N Engl J Med*. 2018;22(21):2040–51. 379(.
 38. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *N Engl J Med*. 2018 May;31(22):2078–92. 378(.
 39. Opdivo for Non-Small. Cell Lung Cancer – Details [Internet]. CADTH.ca. 2015 [cited 2020 Mar 9]. Available from: <https://www.cadth.ca/opdivo-non-small-cell-lung-cancer-details>.
 40. Keytruda for Non-Small Cell Lung Cancer. (Second Line or Beyond) – Details [Internet]. CADTH.ca. 2016 [cited 2020 Mar 9]. Available from: <https://www.cadth.ca/keytruda-non-small-cell-lung-cancer-second-line-or-beyond-details>.

Figures

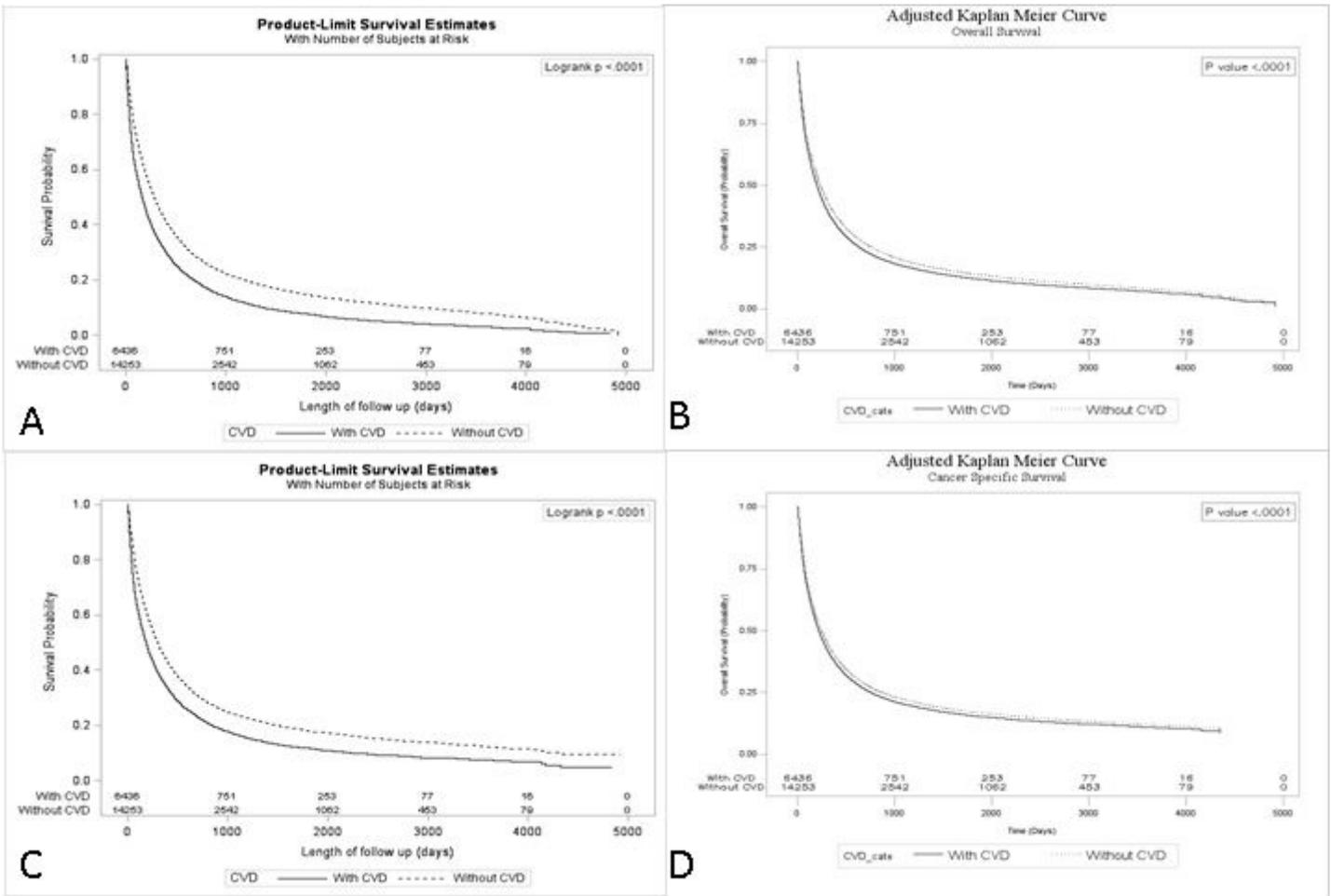


Figure 1

Kaplan-Meier curves showing: A. Unadjusted for overall survival B. Adjusted for overall survival C. Unadjusted for cancer specific survival D. Adjusted for cancer specific survival