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Disparities and Determinants of Cardio-Cerebrovascular Mortality in Middle Aged Patients With Lung Cancer: a population based SEER cohort study, 2000-2021

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Abstract

Background:

Advances in lung cancer detection and treatment have improved survival, increasing the relative importance of non-cancer causes of death, particularly cardiovascular and cerebrovascular disease. However, data on cardio-cerebrovascular mortality (CCM) among middle aged patients remain limited.

Methods:

We analyzed patients aged 30 to 59 years with pathologically confirmed lung cancer from the Surveillance, Epidemiology, and End Results (SEER) 17 registries (2000–2021). CCM was defined as death due to cardiovascular or cerebrovascular causes. Kaplan–Meier analyses and Cox proportional hazards models were used to evaluate outcomes and identify predictors.

Results:

Among 185,296 patients, CCM occurred in 2.2%. Incidence increased with age, reaching 2.59% in patients aged 55–59 years. Ischemic heart disease accounted for 51% of CCM events, followed by cerebrovascular events (15.1%). Advanced stage disease was associated with higher CCM risk (stage III: HR 1.58, $p = 0.001$; stage IV: HR 1.64, $p < 0.001$). Squamous cell carcinoma was associated with a higher risk compared with adenocarcinoma (HR 1.56, $p < 0.001$). Non-Hispanic Black patients had significantly higher CCM risk (HR 2.54, $p < 0.001$). Socioeconomic factors were not independently associated with CCM.

Conclusions:

CCM in middle aged patients with lung cancer increases after age 50 and is associated with advanced stage, squamous histology, and Non-Hispanic Black race. These findings highlight the need for targeted cardio-oncology surveillance and preventive strategies in high-risk populations.

Trial registration

Not applicable

Background

Lung cancer is one of the cancers with high mortality and the most common cancer worldwide. (1) Advances in early detection, molecular profiling, targeted therapies, and immunotherapy have improved

survival rates for patients, resulting in many living beyond their initial diagnosis. (2, 3) As survival increases, non-cancer causes of death are becoming more prominent, particularly cardiovascular and cerebrovascular disease. (4, 5)

Cardio-cerebrovascular mortality (CCM) in lung cancer reflects the combined effects of shared risk factors, tumor biology, and treatment-related toxicity. Tobacco exposure, a primary cause of lung cancer, also contributes to atherosclerosis, endothelial dysfunction, and vascular inflammation. (6) Malignancy further promotes a prothrombotic and inflammatory state that increases the risk of arterial thromboembolic events, including myocardial infarction and ischemic stroke. (7) Cancer therapies add to this risk; platinum-based chemotherapy has been linked to endothelial injury and accelerated vascular disease, while thoracic radiotherapy can lead to long-term vascular fibrosis and coronary artery damage. (8, 9)

Tumor characteristics also influence cardiovascular risk. Advanced stage lung cancer is associated with systemic inflammation, metabolic disruption, and greater exposure to cardiotoxic treatments, all of which may increase susceptibility to ischemic events. (10) Histologic subtype is similarly relevant. Squamous cell carcinoma, closely associated with tobacco use, is often accompanied by chronic pulmonary and cardiovascular comorbidities, including chronic obstructive pulmonary disease. (11) These features may contribute to higher cardiovascular mortality compared with other subtypes.

There is growing recognition of cardiovascular risk in oncology populations, but data on CCM among middle aged patients with lung cancer is still limited. Individuals aged 30 to 59 years have lower baseline cardiovascular risk than older adults but may experience accelerated vascular injury related to cancer and its treatment. Cardiovascular aging, including arterial stiffness and vascular remodeling, begins to accelerate during midlife and may increase vulnerability to adverse events. (12–14) In addition, racial and ethnic disparities in cardiovascular outcomes are well established in the general population but remain incompletely characterized in younger patients with lung cancer. (15–17)

A clearer understanding of CCM in the younger patients is important for improving the survival rate, identifying high risk groups, and guiding preventive strategies. This study evaluated the incidence, patterns, and determinants of cardio-cerebrovascular mortality (CCM) among adults aged 30 to 59 years with lung cancer using a large population based dataset.

Methods

This study aimed to evaluate the incidence, patterns, and predictors of cardio-cerebrovascular mortality in middle aged patients with lung cancer. This was a retrospective population-based cohort study.

Population data extraction

Using the Surveillance, Epidemiology, and End Results (SEER) 17 registries Nov 2023 Sub (2000 to 2021; Database ID: 2436), we extracted patients' data with 'Malignancy behavior, Known Age' and 'Lung and

Bronchus' site record from ICD-O-3-2023 Revision codes from SEER*Stat software version 9.0.42.0. Regarding specific data, the following were extracted (Race recode, Year of diagnosis, primary site, Histologic type ICD-O-3, ICD-O-3 Hist/behav, derived EOD 2018 T/N/M stages, derived EOD 2018 stage group, derived AJCC 7th edition T/N/M, RX summ—Surg prim site, RX Summ—Scope Reg LN Sur). Within this cohort, patients aged 30 to 59 years with pathologically confirmed lung cancer were only included for further analysis. Demographic, socioeconomic, tumor characteristics, and treatment variables were also obtained.

The SEER database provides detailed information regarding the cause of death whether it is attributable to primary cancer or not. Based on this information, the primary outcome was cardio/cerebrovascular mortality (CCM), defined as death due to cardiovascular or cerebrovascular causes, including ischemic heart disease, aortic pathology, hypertensive disease, cerebrovascular stroke, pulmonary hypertension, and other vascular causes. The total incidence of CCM by specific causes was analyzed using proportional analyses. The secondary outcome was overall survival, and risk factor for CCM was also evaluated.

Statistical analysis

Statistical analyses were performed using R version 4.3.0 (R Core Team, Vienna, Austria). Categorical variables were analyzed using Chi-square and Fisher's exact tests as appropriate. Continuous variables were assessed using the Wilcoxon Rank Sum test. Survival outcomes were analyzed using Kaplan-Meier estimates and Cox proportional hazards models, and the proportional hazards assumption was verified using time-varying coefficients. Kaplan-Meier curves with log rank tests compared CCM across demographic and clinical strata. Univariate and multivariable Cox proportional hazards models identified independent predictors of CCM. Variables with a p-value less than 0.10 in univariate analysis were used for multivariable analysis. To compare the incidence of CCM by age groups, a proportion analysis with 95% confidence interval was used.

Results

Characteristics of study populations

A total of 185,296 patients met the inclusion criteria. Table 1 described the general characteristics of the entire cohort. Nearly half were aged 55 to 59 years (49.8%), and 71.4% were Non-Hispanic White. Adenocarcinoma was the most common histology (59.3%), followed by squamous cell carcinoma (21.5%) and small cell cancer (19.2%). More than half of patients presented with stage IV disease (53.5%). In terms of socioeconomic factors, about half of patients resided in a large metropolitan area with a population over 1 million, and about 60% of patients had an annual household income less than 80,000 dollars.

Table 1
Baseline Characteristics of the Study Population

Characteristic	Category	n (%)
Age group (years)		Total N = 185296
	30–34	1,471 (0.8)
	35–39	3,653 (2.0)
	40–44	10,193 (5.5)
	45–49	25,038 (13.5)
	50–54	52,590 (28.4)
	55–59	92,351 (49.8)
Histology	Adenocarcinoma	77,942 (59.3)
	Small cell	25,237 (19.2)
	Squamous	28,240 (21.5)
Diagnosis of lung cancer	Before 2015*	135,819 (73.3)
	2015 and after	49,477 (26.7)
Race/ethnicity	Hispanic (all races)	11,569 (6.2)
	American Indian/Alaska Native	1,132 (0.6)
	Asian/Pacific Islander	12,380 (6.7)
	Black	27,884 (15.0)
	White	132,331 (71.4)
Stage	I	7,652 (20.1)
	II	2,497 (6.6)
	III	7,551 (19.8)
	IV	20,387 (53.5)
Annual Income (SDOH)	<$40,000	5,347 (2.9)
Data is presented as n (%)		
CCM, cardio-cerebrovascular mortality; SDOH, Social Determinants of Health.		
* Immunotherapy was approved by FDA in 2015		
§ metropolitan-small means population under 1 million, and metropolitan-large means population above 1 million		

Characteristic	Category	n (%)
	$40,000 - $80,000	111,062 (59.9)
	$80,000 - $120,000	63,410 (34.2)
	>$120,000	5,466 (3.0)
Area (SDOH)§	Non-metropolitan area	32,688 (17.7)
	Metropolitan - small	55,784 (30.2)
	Metropolitan - large	96,502 (52.2)
Chemotherapy	No/Unknown	81,970 (44.2)
	Yes	103,326 (55.8)
Surgery	No/Unknown	134,786 (74.2)
	Yes	46,943 (25.8)
Radiation	No/Unknown	100,566 (54.3)
	Yes	84,740 (45.7)
Overall mortality		148,394 (80.1)
CCM		4,159 (2.2)
CCM specific causes		
	Ischemic heart disease	2122 (51)
	Cerebrovascular accident	627 (15.1)
	Hypertensive related problems	169 (4.1)
	Pulmonary hypertension	163 (3.9)
	Aortic and vascular issues	69 (1.7)
Data is presented as n (%)		
CCM, cardio-cerebrovascular mortality; SDOH, Social Determinants of Health.		
* Immunotherapy was approved by FDA in 2015		
§ metropolitan-small means population under 1 million, and metropolitan-large means population above 1 million		

Outcomes and risk factor analysis

Regarding treatments, about half of the patients had chemotherapy (55.8%), and a quarter of the cohort had surgical treatments (25.8%). In addition, about half of patients (45.7%) had radiation treatment but

SEER lacks detailed information on radiation fields, limiting interpretation of radiation associated cardiovascular risk.

Overall, CCM occurred in 2.2% of patients (n = 4,159) and there was a significant difference per cancer stages (Fig. 1). Overall survival was significantly affected by cancer stages. In terms of specific causes of CCM, Ischemic heart disease accounted for most CCM events (51.0%), followed by cerebrovascular events, including ischemic and/or hemorrhagic stroke (15.1%).

Risk factor analysis for CCM was performed using Cox proportional hazard regression (Table 2). Multivariate analysis revealed that stage/histology subtypes/race/SDOH-related factors were significantly associated with it. Stage III (HR 1.58, $p = 0.001$) and stage IV (HR 1.64, $p < 0.001$) were both significant predictors. Squamous cell carcinoma also elevated CCM risk relative to adenocarcinoma (HR 1.56, $p < 0.001$). Non-Hispanic Black patients experienced more than twice the hazard of CCM compared with other racial groups (HR 2.54, $p < 0.001$). However, socioeconomic indicators, including household income and urban-rural classification, were not independently associated with CCM.

Table 2
Multivariable analysis for cardiovascular/cerebrovascular mortality in middle aged patients diagnosed with lung cancer.

Variable	Hazard Ratio	95% confidence interval	p-value
Income			
Income under $40,000	Reference		
Income $40,000–$80,000	1.05	0.61–1.78	.87
Income $80,000–$120,000	0.91	0.51–1.62	.75
Income >$120,000	0.95	0.45–2.00	.90
Area*			
Non-metropolitan	Reference		
Metropolitan-small	0.96	0.73–1.27	.79
Metropolitan-large	0.79	0.59–1.07	.12
Stages			
Stage I	Reference		
Stage II	1.37	0.93–2.00	.11
Stage III	1.58	1.19–2.10	.002
Stage IV	1.64	1.25–2.14	< .001
Histology			
Adenocarcinoma	Reference		
Small cell	1.29	0.98–1.69	.071
Squamous	1.56	1.24–1.96	< .001
Race/Ethnicity			
Hispanic	Reference		
American Indian/Alaska Native	1.84	0.43–7.95	.41
Asian/Pacific islander	1.05	0.57–1.91	.88
Black	2.54	1.53–4.21	< .001
HR, Hazard ratio; CI, Confidence interval			
* metropolitan-small means population under 1 million, and metropolitan-large means population above 1 million			

Variable	Hazard Ratio	95% confidence interval	p-value
Income			
White	1.63	1.01–2.63	.046
HR, Hazard ratio; CI, Confidence interval			
* metropolitan-small means population under 1 million, and metropolitan-large means population above 1 million			

Furthermore, the incidence of CCM increased substantially with age, from 1.29% among individuals aged 30 to 49 years to 2.12% at ages 50 to 54 and 2.59% at ages 55 to 59 (Table 3).

Table 3
Incidence of cardio/cerebrovascular mortality by age group.

Age Group (yr)	Incidence per 100 patients	95% CI
30–34	1.29	0.78–2.01
35–39	0.99	0.69–1.36
40–44	1.52	1.29–1.78
45–49	1.76	1.60–1.93
50–54	2.12	2.00–2.24
55–59	2.59	2.49–2.70
CI, Confidence interval.		

Discussion

Among middle aged patients with lung cancer, cardio-cerebrovascular mortality (CCM) increased after age 50 and was associated with advanced-stage, squamous cell carcinoma type, and those identifying as non-Hispanic Black. These findings emphasize the complex interplay between cancer biology, host physiology, and cardiovascular vulnerability in the setting of lung cancer. To the best of our knowledge, this is one of the largest population based studies evaluating cardio-cerebrovascular mortality in middle aged patients with lung cancer. It delivers valuable information and helps identify high risk groups so that clinicians can improve the outcomes.

Advanced stage lung cancer is associated with greater systemic inflammation, endothelial dysfunction, and plaque destabilization that promote ischemic cardiovascular and cerebrovascular events. (10) Patients with advanced disease are more frequently exposed to cardiotoxic systemic therapies, including platinum-based chemotherapy and thoracic radiotherapy. (8, 9) Cancer-related hypercoagulability,

thrombosis, and cachexia further increase cardiovascular stress and mortality risk. (18, 19) These mechanisms plausibly explain the higher CCM observed in advanced-stage disease.

Squamous-cell carcinoma (SCC) is strongly associated with tobacco exposure, a shared risk factor for both lung cancer and cardiovascular disease. (6) SCC is also commonly accompanied by chronic obstructive pulmonary disease and pulmonary vascular disease, increasing cardiopulmonary strain and cardiovascular mortality. (11) Because SCC frequently arises in central airways, hypoxemia and cardiopulmonary compromise may predispose to arrhythmias and ischemic events. (20–23) Molecular profiling studies additionally demonstrate inflammatory and immune-active SCC subtypes that may contribute to systemic vascular dysfunction. (24, 25) Therefore, further investigation of cardiovascular risk factors would be beneficial to patients with SCC.

Cardiovascular aging accelerates after midlife due to progressive central arterial stiffening, vascular calcification, and arterial elastic loss. (12–14) Arterial stiffness increases with age and independently predicts cardiovascular morbidity and mortality. These changes contribute to systolic hypertension and widen pulse pressure and, together with the accumulation of traditional cardiovascular risk factors, likely increase susceptibility to CCM after age 50. (12, 13) Though proportional benefits of age in this study were not obvious, age should always be considered as a significant clinical factor to monitor even the younger patients with lung cancer.

Non-Hispanic Black adults experience a disproportionate burden of hypertension and vascular disease, characterized by higher central blood pressures, greater salt sensitivity, and reduced nitric oxide bioavailability, all of which contribute to increased cardiovascular risk. (15–17) In oncology populations, Non-Hispanic Black patients may also experience higher rates of treatment-associated cardiac injury. (26) These findings may help explain why Non-Hispanic Black patients with lung cancer require close cardiovascular monitoring.

There are several limitations in this study. First, there is limited access to specific patient-level data, such as complications, medication history, and detailed information on causes of death. This is inevitable in the setting of a population database. Though the study cohort was limited to individuals aged 30 to 59 to avoid potential confounding from preexisting conditions, clinicians should be cautious when applying our findings to make decisions for individual level of care, as multiple sources of bias may exist. Second, treatment specific data were limited. Previous literatures frequently mentioned cardiotoxicity from platinum-based chemotherapy as well as checkpoint inhibitors. Also, further information regarding radiation therapy was limited; for example, it was hard to distinguish whether the patient received cranial or chest radiation. This could explain why the radiation therapy was not found to be significant for CCM. Third, it is still a retrospective study even though we included the largest cohort in this topic. These findings emphasize the need for early cardiovascular surveillance and risk stratification in high risk subgroups of patients with lung cancer.

Conclusion

CCM in middle aged patients with lung cancer increases after age 50 and is highest among patients with advanced-stage disease, squamous histology, and Non-Hispanic Black race. These findings support the integration of structured cardiovascular risk assessment and targeted preventive strategies into routine oncology care to improve long-term survivorship.

Abbreviations

CCM
Cardio–cerebrovascular mortality
SEER
Surveillance, Epidemiology, and End Results
HR
Hazard ratio

Declarations

Ethics approval and consent to participate

This study utilized de-identified data from the SEER database and was exempt from institutional review board approval.

Consent for publication

Not applicable

Funding

No funding was received for this study

Author Contribution

YL contributed to the conception and design of the study, data acquisition, statistical analysis, interpretation of the data, and drafting the manuscript. AK contributed to the study design, data interpretation, and manuscript revision. AS and WW supervised the study, contributed to the study design and interpretation of the findings, and revised the final manuscript. All authors reviewed and approved the final manuscript.

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None

Data Availability

Surveillance, Epidemiology, and End Results (SEER) 17 registries (2000–2021)

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releases%2f2023%2f04%2f14%2f13%2f46%2fblack-cancer-patients-71-more-likely-to-experience-heart-damage-following-chemotherapy-treatment

Figures

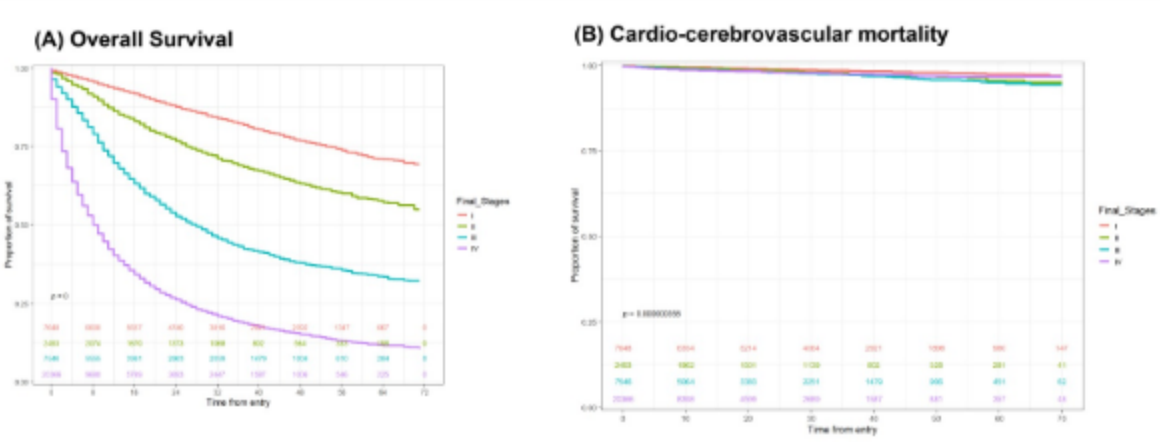

Figure 1

Kaplan-Meier survival curves for (A) overall survival and (B) cardio-cerebrovascular mortality according to lung cancer stage.