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Long-Term Pre-Diagnosis Exposure to Ambient Air Pollution and Weather Conditions and Their Impact on Survival in Stage 1A Non-Small Cell Lung Cancer: A U.S. Surveillance, Epidemiology, and End Results(SEER)-Based Cohort Study

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Abstract: Background: Ambient air pollution is a modifiable determinant of lung cancer survival, affecting early-stage Non-Small Cell Lung Cancer (NSCLC) incidence and mortality. Methods: This retrospective cohort study examined the association between all-cause mortality and exposure to air pollution among stage 1A NSCLC-treated patients from the U.S. National Cancer Registry from 1988 to 2015. The Cox hazard model and Kaplan–Meier survival plots were provided. Air pollutants were included separately and together in the models, accounting for spatiotemporal weather variability affecting air pollution exposure levels pre and post lung cancer diagnosis. Results: NO_2 (above the median sample mean = 25.66 ppb; 12.97 ppb below median), SO_2 (above median sample mean = 3.98 ppb; 1.81 ppb below median), and CO (above median sample mean = 1010.84 ppb; 447.91 ppb below median) air pollutant levels and weather conditions were calculated for county-day units. The median months of survival for those exposed to above-median NO_2 were 27 months (SD = 17.61 months), while the median was 30 months (SD = 15.93 months) for those exposed to below-median levels. Multipollutant analyses indicated that an average monthly NO_2 increase of 1 part per billion (ppb) in the county of NSCLC diagnosis was associated with increases of 4%, 6%, and 9% in the all-cause mortality rate one, three, and five years after diagnosis, respectively; an equivalent increase in SO_2 was associated with increases of 16%, 17%, and 17%; and an increase in CO was associated with increases of 53%, 51%, and 42% Conclusion: It is vital to implement environmental policies that control emissions to reduce preventable deaths in stage 1A NSCLC patients with adenocarcinoma or squamous cell carcinoma histology types who reside in metropolitan areas.

Keywords: air pollutants; weather; NSCLC; SEER; survival analysis

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1. Background and Study Rationale

Several modifiable social determinants of health (SDOH) that improve lung cancer survival exist beyond smoking cessation [1–3]. Ambient air pollution is a modifiable determinant of lung cancer survival [4–6], and yet research exploring the dose–relationship association between ambient air pollution and lung cancer incidence and mortality in the United States (U.S.) is limited [3,5–7]. Air pollutants affect a specific type of lung cancer histology [6,8–10]; therefore, it is essential to focus specifically on histology type and

specific clinical stages of lung cancer to determine survival outcomes [3,5], although only a few studies attempt to take this into account. Only one study to date has established a dose–response relationship between localized lung cancer survival and ambient air pollution exposure [3], but the study did not account for weather components that might affect exposure levels within the vicinity [11–14].

Air pollutant levels differ geographically, affecting the level of exposure among patients in longitudinal studies. Changes in weather conditions also facilitate chemical reactions between primary pollutants (NO_2, SO_2, CO, and PM) and other atmospheric chemicals, resulting in secondary pollutant production. The weather components, such as maximum temperature, are also correlated with air pollutants, as an increase in air pollutants aids in the urban heat island phenomenon [15]. Hence, secondary pollutants such as ozone and weather components such as maximum temperature might lead to biased estimation results in a given study context. Therefore, it is vital to understand the complex interaction of air pollutants in the presence of weather conditions, such as precipitation, snow, and temperature, which affect the specific exposure levels and determine the survival outcomes of stage 1A TN0M0 NSCLC [16].

Some studies in the literature that identify the dose–response relationship between ambient air pollution and lung cancer survival utilize interpolation or other data techniques to replace missing pollutant levels [3,5]. The drawback of interpolating or extrapolating missing pollutant values without taking into account other environmental factors is that one might inherently misclassify the levels of exposure, providing uncertain estimates due to the absence of relevant information, such as natural events and weather conditions, such as snow, precipitation and temperature, and their interactions with other spatially and temporally dependent pollutants [11–14,17–19]. Moreover, there is a lack of sufficient attention to the variance in values when utilizing different methods to those of the nearest monitoring stations to assign exposure values and determine health outcomes [13].

As per recent studies, the optimization of the monitors and their location utilizing the Operational Street Pollution Model (OSPM) facilitates the accurate monitoring of air pollution levels and accurate data collection, as it incorporates spatiotemporal variability [20]. This helps to inform environmental policies more efficiently, as the measurements contain fewer errors. The United States Environmental Protection Agency (US EPA) collects and monitors U.S. counties' air pollution data and utilizes a similar modeling technique to provide spatiotemporally accurate exposure data using varied modeling techniques [21–23]. Some of the modeling techniques it utilizes to optimize monitor locations and monitoring are AERMOD (American Meteorological Society/Environmental Protection Agency Regulatory Model), the Community Multiscale Air Quality Model (CMAQ), CALPUFF, Air Quality System (AQS) Network Design Criteria, and the Air Sensor toolbox, which provide varied accuracy monitoring and data collection techniques that range from predicting pollutant dispersion from stationary sources at the local scale (up to 31 miles) and the use of regional air-quality models simulating ozone, particulate matter, and other pollutants over large areas to siting low-cost sensors and supplementing regulatory monitors based on traffic, land use, and public exposure. Utilizing the nearest monitoring technique on the basis of the data collected by US EPA monitors can partially account for the spatiotemporal distribution in the presence of weather conditions.

Several factors affect the standard care and treatment that is received, an important confounder in determining survival outcomes for stage 1A NSCLC [24–27]. The National Comprehensive Cancer Network (NCCN) treatment guidelines are referred to by about 95% of U.S. oncologists to recommend standard treatment. Changes in these guidelines, resulting from revisions in recent decades, may affect those who receive standard care for early-stage lung cancer. Differences in standard treatment receipt exist for early-stage

lung cancer according to the year in which the treatment guidelines were revised, race, geography, and insurance status, as established in an extended prior study [28]. The trends in the type of treatment and air pollution levels thatare spatially and temporally dependent on the presence of weather elements, identified over a more extended study period across various US states, could help to more accurately identify the true causal relationships, as reported in similar survival studies [3,29].

Hence, it is also crucial to identify whether ambient air pollution has a dose–response effect on lung cancer survival outcomes depending on the type of treatment received; this requires consideration of the timespan of several US national treatment guideline revisions, the pre-diagnosis exposure values to account for the cumulative effect, and the differential time-invariable confounders in different states and counties in the statistical analysis. To our knowledge, few studies have aim to achieve this for a representative U.S. population [3,5,30], and these studies did not account for the dose–response relationship in the presence of weather components in a homogenous sample of stage 1A NSCLC TN0M0. They also did not account for other primary air pollutants, such as SO_2 and CO. Finally, the studies assigned exposure values from the month of diagnosis to death rather than considering pre-diagnosis exposures. This could lead to their not accounting for the carry-over effect on health outcomes from exposure before diagnosis.

Therefore, we aimed to evaluate whether exposure to specific levels of air pollutants and weather elements both pre- and post-diagnosis for up to five years is associated with survival outcomes among patients with stage 1A TN0M0 non-small cell lung cancer (NSCLC) undergoing their treatment of choice, utilizing U.S. population-based cancer data and U.S. environmental air pollution data. Does accounting for any key confounders that are missing in previous similar studies reduce selection bias and provide close-to-true hazard ratios? How does treatment choice affect survival outcomes in the presence of exposure to the identified air pollutants? We hypothesize that there is a difference in all-cause mortality among treated individuals exposed to high versus low air pollution levels [3].

2. Methods

2.1. Study Design

This retrospective cohort study compared the survival outcomes between patients exposed to higher versus lower levels of air pollution and those receiving different treatment types (i.e., limited resection with adjuvant radiotherapy and lobectomy) in single- and multi-pollutant models similar to those in the limited pre-existing studies [3,30]. The pollutant model included NO_2, SO_2, and CO, adjusted for precipitation, snow, and daily minimum temperature values in both the single-pollutant and multi-pollutant models. The multi-pollutant model included NO_2, SO_2, and CO, along with weather components, whereas the single-pollutant models consisted of one primary pollutant and weather components. The pollutant models were analyzed separately for three time intervals (one, three, and five years) in the pre-diagnosis exposure model, and for one year, three years, and five years of survival outcomes (post-diagnosis exposure) to determine the robustness of the estimates [5,7].

2.2. Data Sources and Construction of the Analysis Data File

The SEER 18 Research Plus, environment data, and AHRF from 1988 to 2015 were used. The SEER 18 Research Plus data access request was approved on 18 April 2022, with reference number SAR0028589; the data were accessed through the SEER*Stat account. The AHRF collects data from over 50 national sources, aggregated at the county level, and the data are compiled by the Health Resources and Services Administration's (HRSA)

Bureau of Health Professions for each of the nation's counties using publicly available data. The Surveillance Research Program (SRP) of the National Cancer Institute (NCI) Division of Cancer Control and Population Sciences (DCCPS) supports SEER. SEER collects and publishes cancer incidence and survival data for every cancer case reported in 22 U.S. geographic areas, covering approximately 48 percent of the U.S. population, through population-based cancer registries. Registries routinely collect data on patient demographics, primary tumor site, tumor morphology, and stage at diagnosis, as well as the first course of treatment and follow-up for vital status (survival) [31,32].

Agency-pregenerated daily summary air pollutant data files from 1988 to 2015 were downloaded from the following website: https://aqs.epa.gov/aqsweb/airdata/download_files.html accessed on 25 November 2021. The raw data that were downloaded regarding air pollutants included ground-level ozone (O_3), sulfur dioxide (SO_2), carbon monoxide (CO), and nitrogen dioxide (NO_2). The raw data downloaded for particulate pollutants were particulate matter ($PM_{2.5}$ and PM_{10}). We initially investigated the toxic precursor benzene in hazardous air pollutants (HAPs) and volatile organic compounds (VOCs); however, the high rates if missing values made it unfeasible to include these data in the final data analysis file. The raw data files for weather were retrieved using the following link https://www.ncei.noaa.gov/data/global-historical-climatology-network-daily/ accessed on 25 November 2021. Zip files from 1988 to 2015 were downloaded for each year and unzipped to retrieve the raw files.

The construction of the data file for the final analysis is shown in Figure 1, and the sample selection process is presented in Figure 2. AHRF files were converted from software-independent archival files to software-dependent files and subsequently cleaned before being merged with SEER data, using the year and county Federal Information Processing Standard (FIPS) code as the merging criterion. Similarly, after conducting data-quality procedures, i.e., excluding duplicates, coordinate error correction, date format standardization, and aggregating monthly averages on weather and air pollution data files for the study period, the data were assigned to SEER registry patients according to the nearest monitoring station method, as explained in the exposure assignment section of this paper.

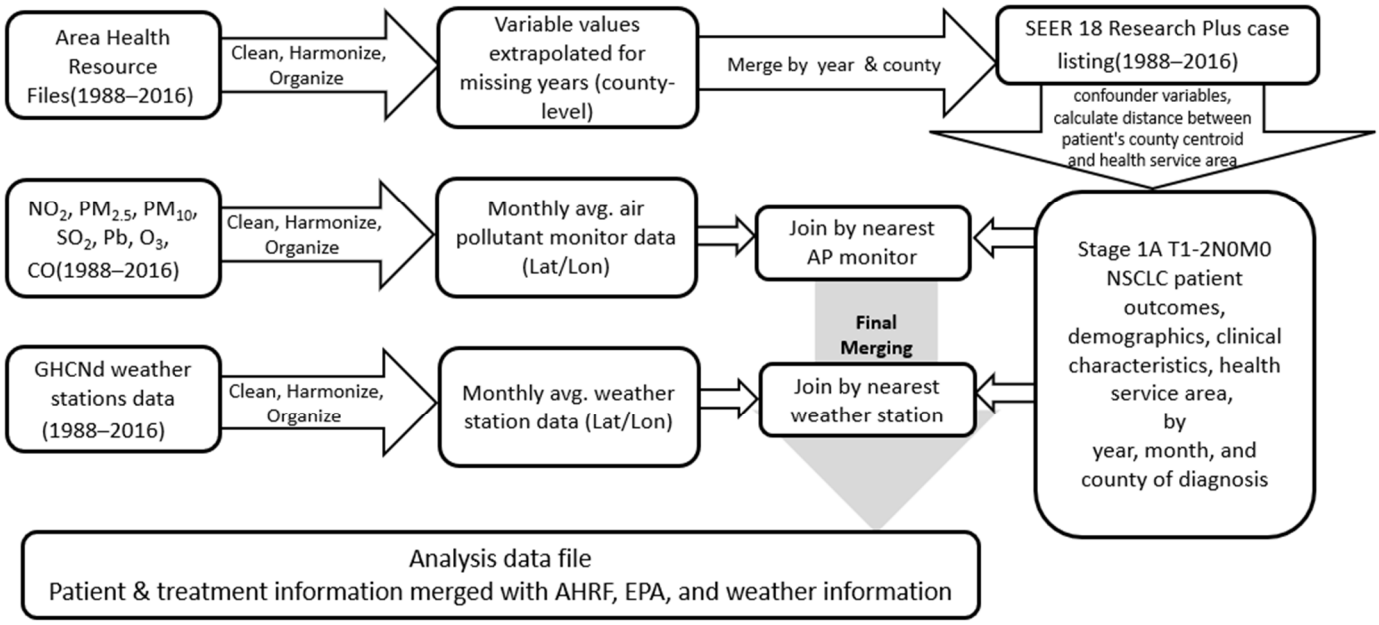


Figure 1. Data analysis file construction.

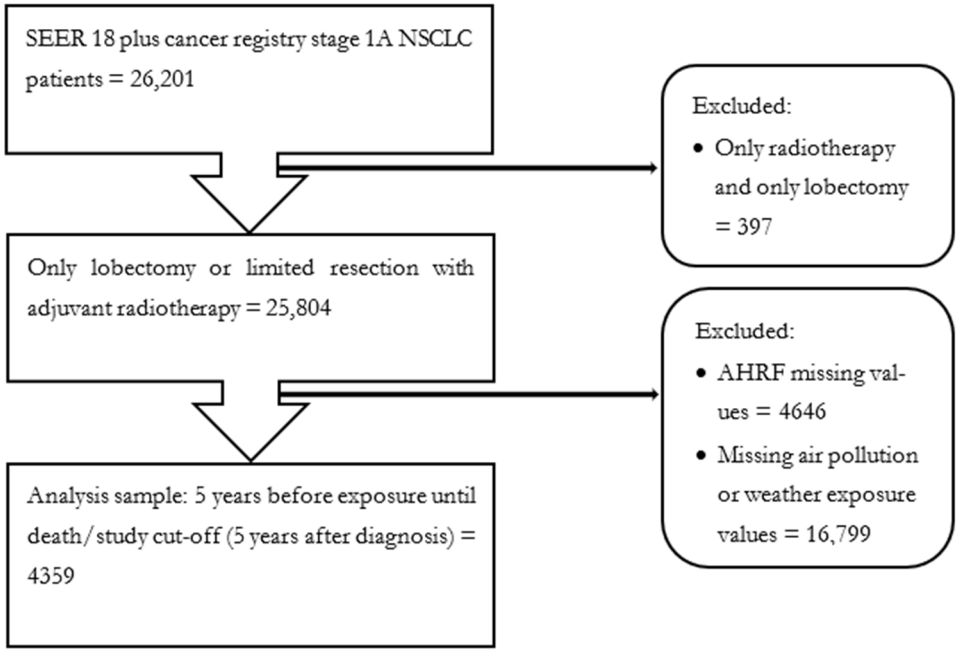


Figure 2. Final study sample using SEER 18 research and cancer registry data; an extension of prior work [28].

2.3. Methodological Framework

Descriptive statistics, Kaplan–Meier survival graphs, and the Cox regression model [3,5,7,30] were used to determine the sample demographics and time to all-cause mortality, with data being excluded due to death or study end. The model examined the association between treatment types, air pollutants, weather, and survival, as well as the interactions between treatment types and air pollutants and between weather and treatment types, while adjusting for patient demographics, clinical characteristics, and time-invariant unobserved variables, including the year of diagnosis and county FIPS. The duration dependence of hazards due to unobserved heterogeneity was accounted for in the model through including the year of diagnosis and county-specific, time-invariant, unobservable factors. Single-pollutant and multi-pollutant models were computed, adjusting for the same covariates and dummy variables to determine whether the estimates were biased due to the independent variables that were omitted in the unadjusted model. The final model was examined regarding the diagnostic criteria and model fit, including testing for multicollinearity between the exposure variables. The omitted variable bias (OVB) and correlation matrix analysis further showed variables that posed a multicollinearity problem regarding the key independent air pollutant exposure coefficients. After the preliminary analysis and diagnostics, the final regression models included NO_2, SO_2, CO, precipitation, daily minimum temperature, and snow accumulation variables.

Kaplan–Meier survival curves and dose–response relationships between adjusted NO_2, SO_2, and CO hazards were plotted using pollutant quartile groups [5] to determine survival probabilities and dose–response relationships. Survivor functions according to pollutant groups were plotted using the data from the nearest air pollution monitors for up to 30 miles. The weather station 20 miles away was missing 25% of its monthly values for this range, while when trying to measure air pollution up to 40 miles away, the weather station was missing 50% of its monthly values [3,5]. STATA 16 and Microsoft Excel released in 2021 were used for the data analysis.

The following empirical model analyzes the survival outcomes for patients treated with fixed-effect dummy variables:

$$H(t) = h_0(t).\exp\{\beta_1.Treatment\ Type_i + \beta_2.Patient\ Demographics_i + \beta_3.Clinical\ Characteristics_i + \beta_4.County_i + \beta_5.Air\ Pollutants_i + \beta_6.Weather\ Components_i + \beta_7.Air\ Pollutants_i \times Treatment\ Type_i + \beta_8.Weather\ Components_i \times Treatment\ Type_i + \beta_9.Year\ of\ Diagnosis_i\}$$

where h0(t) is the baseline hazards and exp(βs) is the hazard ratio or rate ratio. The variables of $county_i$ and $year\ of\ diagnosis_i$ are county- and year-of-diagnosis time-invariant, unobservable factors. In the model, i indicates an individual patient. "Treatment Type" is a binary variable that takes the value "lobectomy" if the patient underwent a lobectomy and "limited resection with adjuvant radiotherapy" if the patient underwent a limited resection with adjuvant radiotherapy. Other treatment types were excluded because there were fewer observations within the radiotherapy and limited resection categories.

2.4. Sensitivity Analyses

The effect's robustness was tested by estimating hazards using the average monthly median and maximum exposure values for one, three, and five years before and after diagnosis, obtained from the corresponding daily exposure values. The confounding effect due to omitted exposure variables was assessed by running both single-pollutant and multi-pollutant models.

2.5. Ethical Considerations

The University of Louisville ethics committee approved this study (IRB number 22.0281). The study is exempt under 45 CFR 46.101(b) in Category 4: secondary research, for which consent is not required.

2.6. Sampling Strategy, Exposure Assignment, and Study Variables

2.6.1. Population and Sample

The SEER 18 research and the inclusion and exclusion criteria for the cancer registry patients are explained in a prior published work [28], while the final included study sample is described in Figure 2 of the current paper. The final sample included patients with monthly exposure averages calculated from daily air pollution values and weather data, and the percentage of missing values for non-missing variables in the regression analysis, in addition to the AHRF and SEER 18 files. The inclusion and exclusion criteria for weather and air pollution exposure values are described in the exposure assignment section of this paper. After preliminary analysis, patients who experienced exposure up to five years before diagnosis were included in the final analysis and followed until death or the study cutoff from the date of diagnosis to five years after diagnosis. The reason for including these patients was to mitigate the compositional effect and the misspecification error resulting from migration during the more extended study periods. If including patients five years after diagnosis and five years before diagnosis, the exposure period is too long, comprising a time frame that is more prone to migration. According to the U.S. Census Bureau's mobility data from 2017 to 2021, approximately 4% and 2% of people aged 25–64 and 65, respectively, migrate to a different county. The information on the excluded sample of the study is provided in Appendix A Table A1a,b.

2.6.2. Exposure Assignment

Air pollution and weather exposure assignments for each patient are shown in Figure 3. We utilized the nearest monitor station method to assign pollutant concentration exposure values using the closest monitor to each study participant's location from the county centroid and included the values of the three nearest neighboring monitors in the event one of the nearest monitors had a missing value for a given day, in which case the data from the second and third nearest monitor were utilized to assign exposure values [3,5,33]. The exposure levels of each patient in the final sample were measured until death or study cut-off (ten years after diagnosis) and from one, three, five, and ten years before diagnosis. Exposure assignments were excluded when the nearest air pollution monitoring station was more than 40 miles away, the weather station was more than 20 miles away, and the percentage of missing monthly values exceeded 50%. A preliminary sample analysis of the exposure assignments for air pollution $\leq$ 30 miles, weather $\leq$ 10 miles, and <33.33% missing values determined the minimal sample size; therefore, the final analysis sample was the least restrictive in terms of the distance of the air pollution exposure assignments from the nearest monitoring station: <40 miles, with a weather station within $\leq$20 miles, and missing monthly values of $\leq$50%. The investigators were aware of the measurement error problems this may cause; however, we aimed to retain the study's power by being less restrictive, as measurement errors are inevitable in air pollution epidemiologic studies.

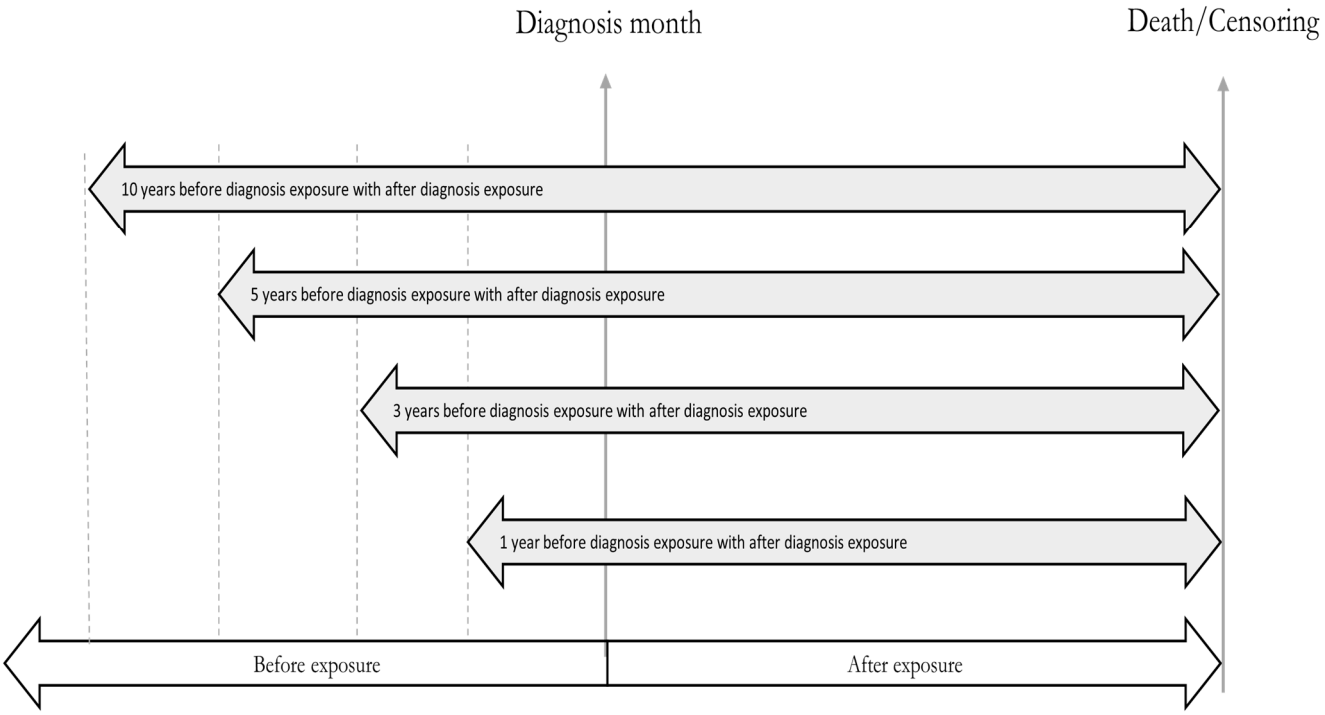


Figure 3. Air pollution and weather exposure value assignment method, including the SEER 18 research and cancer registry patients.

We initially generated the monthly values from the daily values by keeping only those observations that were 10, 20, 30, and 40 miles away from the nearest monitoring station, with 50%, 33.33%, 25%, and 20% missing values for each mile within a month, and the calculated monthly mean, median, maximum, and interquartile range exposure (Figure 4) values for the same for up to 10 years before and 10 years after month of diagnosis or until death. The air pollution exposure at the county-day level was estimated using data from the EPA monitoring stations. We identified the three nearest monitors to each county centroid for each pollutant and calculated the daily average across these stations (Appendix A

Table A1d). The spatiotemporal variability was addressed through several quality assurance steps, including aggregating daily values into monthly measurements (i.e., mean, median, max, and IQR), accounting for temporal variations. As depicted in Figure 4, we generated annual values by aggregating the monthly values into yearly measurements (i.e., mean, median, max, and IQR). Further, we utilized all these annual measurements within multiple nearest-monitor distances (10–40 miles) and varying percentages of missingness tolerance (20–50%) to ensure comprehensive data coverage across time and distance. Finally, weather affects ambient air pollutant levels; hence, we followed similar steps to derive the annual weather elements values. However, we included exposure values in our final analysis, as mentioned previously in this paper.

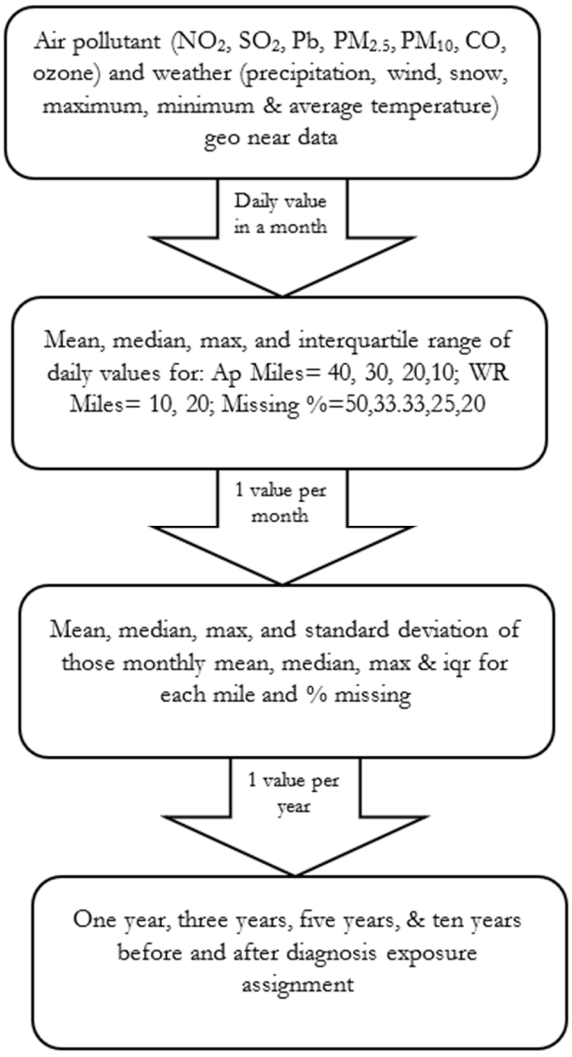


Figure 4. Method for converting the daily air pollution and weather values over a month into a yearly average of monthly values to determine each registered patient's exposure using the nearest monitoring technique.

Exposure assignment errors can be categorized as measurement and misspecification errors. A recent study relevant to the current study determined that long-term exposure assignment measurement errors are inevitable in epidemiological studies and are random. Although randomly present, the classical and Berkson measurement errors obtain biased results towards the null. If the studies find a statistically significant association, the estimates are smaller than the true effect size and are less likely to be undermined [34]. Finally, including exposure assignments for the nearest stations, within <30 miles or ≤20 miles,

would still lead to the measurement error problem, in addition to compromising the study power. The nearest station monitors might capture more accurate values or events, but the average population exposure levels would still differ from individual-level exposure, leading to measurement errors regarding exposure assignment . The latter type of error (i.e., misspecification errors) would also be inevitable in similar studies, as individual patient migration data are absent in national cancer registries, such as the one containing the data in this study. Some measures we took to control for larger misspecification errors restricted the study period to ten years (five years before and five years after diagnosis). An assumption was made regarding the absence of migration during these ten years among the included patients.

2.6.3. Independent Variables

Each continuous variable regarding the weather and air pollution components included the yearly exposure average of the monthly averages before the diagnosis of each patient, up to the time of death or the study cut-off (whichever occurred first). The categorical treatment type variable included two categories: lobectomy and limited resection with adjuvant radiotherapy. Due to the limited number of radiotherapy observations and the few resection cases, it was not feasible to include these two categories in the analysis. Surgery codes for wedge resection and segmentectomy were not differentiated in the data prior to 1998 [35]. Moreover, segmentectomy and wedge resection, as distinct categories, did not have sufficient observations. Hence, we adopted a conservative approach and combined the two types of surgery codes into one category, "Limited Resection", as informed by the NCCN treatment guidelines and similar studies, whose decision was based on the majority of studies establishing no statistical difference between the two types of surgeries and their effect on survival [36,37]. Combining them provided statistical validity and strength to the overall limited resection category. The radiation sequence, including the variable of surgery, was included in the treatment category of limited resection with adjuvant radiotherapy.

2.6.4. Outcome Variable

Survival time was calculated as the number of months of survival from the first diagnosis to death due to any cause (all-cause mortality).

2.6.5. Covariates

Tumor size categories were determined as described by the American Lung Cancer Society (ALCS). Due to the limited number of observations in the category "up to 3 cm" and the absence of specific values, this category was merged with the "unknown tumor size" category. SEER 18 Research Plus cancer registry data lack information on tumor size before 2004, so patients diagnosed before 2004 had missing tumor size values. A more conservative approach was adopted in the current study, and observations with missing information were categorized into the unknown tumor size category. Likewise, no data were available for insurance status information before 2007, so an unknown category was constructed for insurance status information before 2007. Dummy variables for the county FIPS and year of diagnosis were constructed to account for time-invariant unobservable variables. The non-metropolitan rural–urban continuum category comprised small metropolitan, micropolitan, and non-core, as these three categories had limited data, and there was little demographic difference. Hence, the rural–urban continuum categorical variable comprises four categories: large central metro, large fringe metro, medium metro, and non-metropolitan.

3. Results

Overall, individuals exposed to above-median levels of air pollutants had a lower probability of survival than those exposed to below-median levels, as reflected in the Kaplan–Meier survival estimates (Figures 5–7). The single-pollutant model graphs did not appear to exhibit striking differences from their multi-pollutant counterparts, indicating the robustness of the results. Similarly, the air pollution values from the nearest station within 30 miles reflected similar directions of survival probability in terms of both Kaplan–Meier survival estimates and statistical analysis. The dose–response relationship of pollutants was directly compared to the first quartile (Appendix A Figure A1). The hazards were consistently higher with each quartile unit increase in the air pollutant level in the multi-pollutant model. The dose–response relationship was plotted for the mean monthly averages for the NO_2, SO_2, and CO pollutants in a multipollutant model for exposure at one, three, and five years of survival and for exposure five years before diagnosis. Compared to the first quartile, mortality was generally higher for the second, third, and fourth quartiles for all pollutants. For NO_2 and CO pollutants, the relationship seems to be linear. The NO_2 pollutant's second-quartile dose–response relationship, with a 95% confidence interval for three and five years' survival, did not seem to overlap with the third and fourth quartiles. Similarly, the 95% confidence interval for the SO_2 pollutant second-quartile dose–response relationship for three- and five-year survival does not seem to overlap with the third and fourth quartiles. Those exposed to above-median air pollution values were 22.25 ppb for NO_2, 4.10 ppb for SO_2, and 816.75 ppb for CO, as depicted in Table 1b. Those who reside in large metropolitan areas and are White comprise the highest percentage, as depicted in Table 1a.

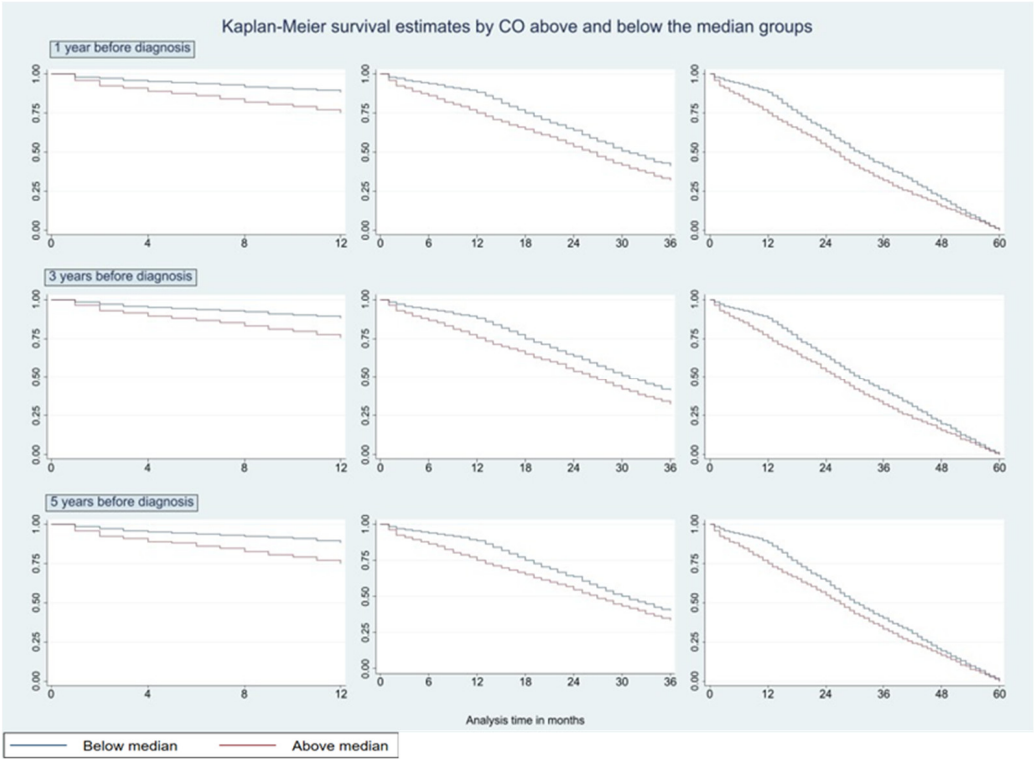


Figure 5. Multi-pollutant model: Kaplan–Meier survival estimates with 95% confidence interval for groups with above- and below-median CO exposure at up to 40 miles distance, with 50% of values missing for one, three, and five years pre–post diagnosis.

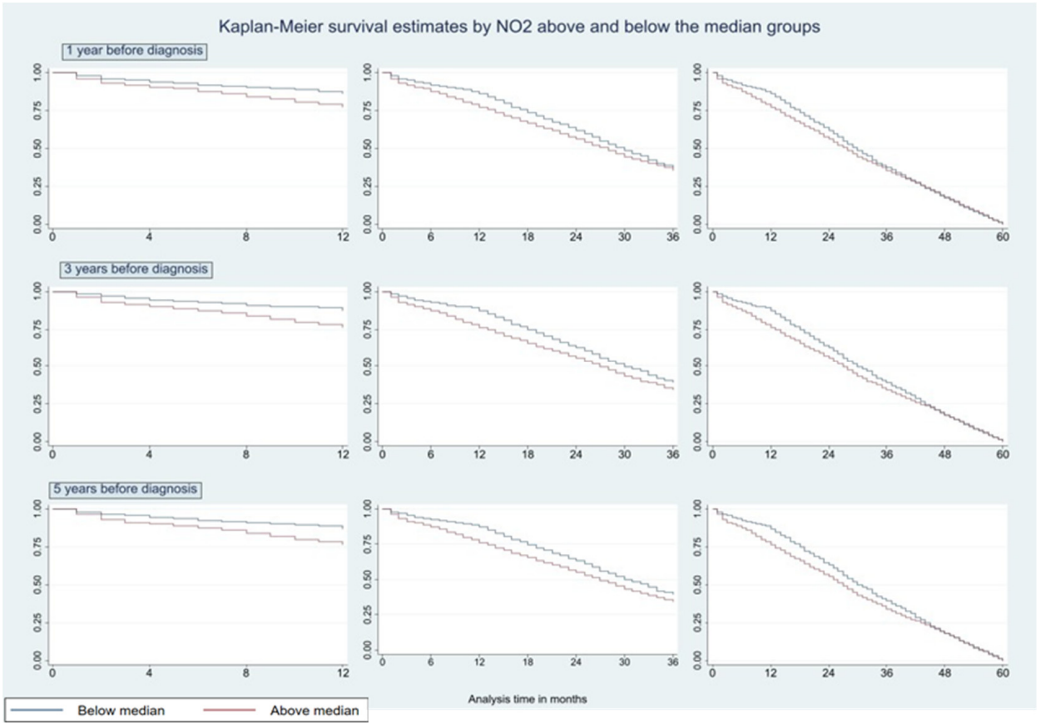


Figure 6. Multi-pollutant model: Kaplan–Meier survival estimates with 95% confidence interval for groups with above- and below-median NO_2 exposure at up to 40 miles distance, with 50% of values missing for one, three, and five years pre–post diagnosis.

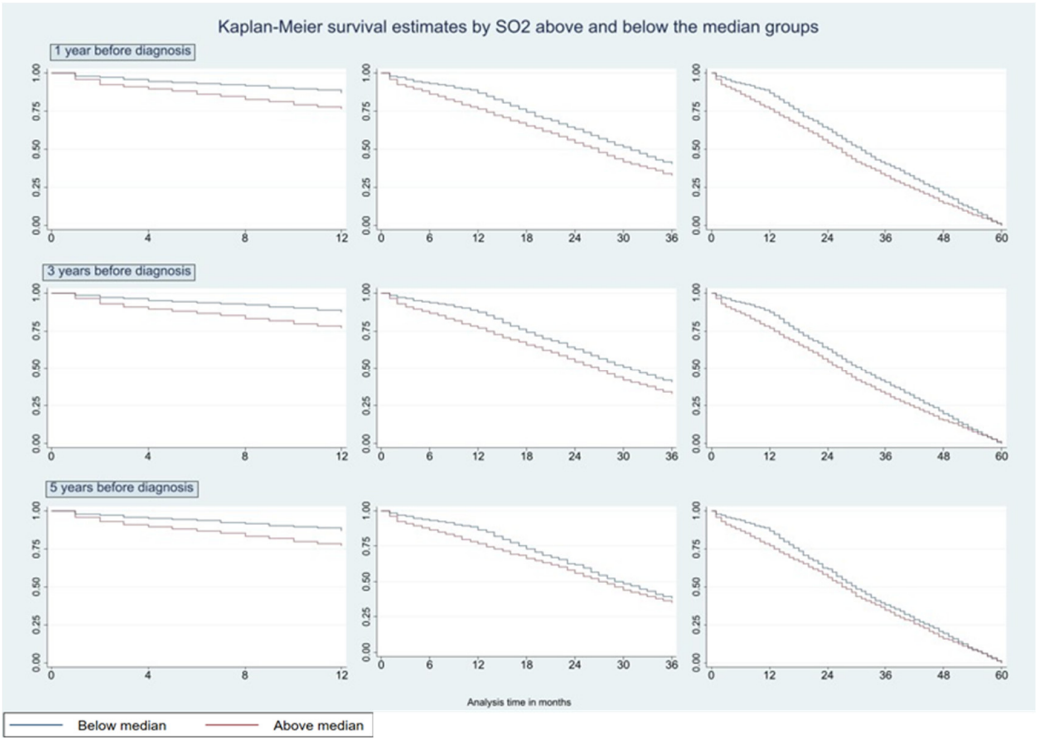


Figure 7. Multi-pollutant model: Kaplan–Meier survival estimates with 95% confidence interval for groups with above- and below-median SO_2 exposure at up to 40 miles distance, with 50% of values missing for one, three, and five years pre–post diagnosis.

Table 1. (**a**) Frequency statistics of the study sample above and below the pollutant exposure median. (**b**) Descriptive statistics of the study sample above and below the pollutant exposure median.

(**a**)				
	Above Median		**Below Median**	
	Frequency	**Percentage**	**Frequency**	**Percentage**
Tumor Grade				
Grade I	262	12.02	484	22.20
Grade II	877	40.25	929	42.61
Grade III	835	38.32	564	25.87
Grade IV	30	1.38	16	0.73
Unknown	175	8.03	187	8.58
Tumor size				
Up to 1 cm	42	1.93	198	9.08
>1 cm and ≤2 cm	208	9.55	820	37.61
>2 cm	189	8.67	643	29.50
Unknown size	1740	79.85	519	23.81
Treatment type				
Only lobectomy	1951	89.54	1815	83.26
Limited resection with adjuvant	228	10.46	365	16.74
Rural–urban continuum				
Large central metro	1333	61.17	1138	52.20
Large fringe metro	536	24.60	801	36.74
Medium metro	285	13.08	195	8.94
Non-metropolitan	25	1.15	46	2.11
Insurance type				
Only Medicaid	35	1.61	125	5.73
Only Medicare	166	7.62	823	37.75
Only Private	69	3.17	468	21.47
Uninsured	6	0.28	16	0.73
Unknown	1903	87.33	748	34.31
Race				
Black	288	13.22	228	10.46
White	1773	81.37	1759	80.69
Unknown	118	5.42	193	8.85
Sex				
Female	969	44.47	1226	56.24
Male	1210	55.53	954	43.76
Marital Status				
Married	1280	58.74	1239	56.83
Widowed	380	17.44	277	12.71
Divorced	247	11.34	284	13.03
Single	224	10.28	278	12.75
Unknown	48	2.20	102	4.68
N	2179		2180	

Table 1. *Cont.*

(**b**)						
	Above median			**Below median**		
	Median	**Mean**	**SD**	**Median**	**Mean**	**SD**
Months of survival	27	28.11	17.61	30	31.09	15.93
Panel A: Exposure to air pollutants before and after diagnosis						
NO_2 exposure (ppb)	22.25	25.66	3.61	12.71	12.97	3.61
SO_2 exposure (ppb)	4.10	3.98	1.20	1.56	1.81	1.20
CO exposure (ppb)	816.75	1010.84	214.13	371.03	447.91	214.13
Panel B: Weather conditions before and after diagnosis						
Precipitation	24.06	26.07	8.76	22.41	23.34	10.93
Snow	0.98	1.14	1.15	0.10	1.28	1.54
Daily minimum temperature	76.04	75.90	17.66	82.80	81.92	18.01
Panel C: individual-level characteristics						
Age at diagnosis	69	67.76	8.52	68	66.38	9.13
Panel D: county-level characteristics						
Population estimates	881,490	3,154,905	3,762,147	933,141	1,281,174	920,018
Unemployment rate	59	63.70	24.39	45	48.85	34.63
Per capita income	30,496	32,920.76	10,118.93	47,146	47,803.63	15,097.07
Total number of hospitals	16	45.68	54.17	13	14.09	9.35
Total number of hospital beds	3797	10,169.78	11,463.38	3130	3184.55	1979.29
N		2179			2180	

The one- and three-year mortality estimates after diagnosis are robust, as indicated in Appendix A Table A4. The all-cause mortality for those exposed to NO_2 increased by 4%, 6%, and 9%, with an average monthly increase of 1 ppb for exposure one, three, and five years before diagnosis, respectively (Table 2 and Appendix A Table A4). Those exposed to SO_2 had an increase in all-cause mortality of 16% and 17%, with an average increase in monthly averages of 1 ppb for exposure one, three, and five years before diagnosis. Those exposed to CO had an increase in all-cause mortality of 53%, 51%, and 42%, with an average increase in monthly averages of 1 ppb for exposure one, three, and five years before diagnosis, respectively. Mortality for those exposed to precipitation decreased by 2% and 3%, with an average monthly increase of one-tenth of a millimeter for one, three, and five years before diagnosis, respectively. Similarly, the mortality for those exposed to snowfall decreased by 10%, with an average monthly increase of one mm for exposure five years before diagnosis. The hazard effect modestly changed the effect size for single-pollutant models; however, the estimates remained significant.

The all-cause mortality for men increased by approximately 13% compared with women for exposure one, three, and five years before diagnosis (Table 2 and Appendix A Table A4). The mortality increased by approximately 10% for those with tumor grade III compared with those with tumor grade II for exposure one, three, and five years before diagnosis, respectively. Mortality decreased by approximately 8% for those with grade I tumors compared with those with grade II tumors. The all-cause mortality decreased by approximately 12% for patients with tumors up to 2 cm in size compared to those with tumors up to 1 cm in size. Compared with Medicaid alone, uninsured patients have increased all-cause mortality by approximately 35% five and three years before diagnosis.

The sensitivity analysis determined a similar direction, size, and statistical significance for these effects, except one year after diagnosis. The effect of the average maximum exposure values for NO_2 and the daily minimum temperature were no longer significant (Appendix A Tables A2 and A3).

Table 2. Mortality five years after diagnosis and effects of annual monthly mean air pollution and weather, as well as treatment type and study covariates.

	Multipollutant	**NO_2**	**SO_2**	**CO**
	Hazards of Death Five Years after Diagnosis			
	Duration of Exposure from Five Years before Diagnosis			
Air pollutants and weather components				
NO_2	1.09 *** (1.06, 1.12)	1.11 *** (1.08, 5.82)		
SO_2	1.17 *** (1.12, 1.21)		1.15 *** (1.10, 1.19)	
CO	1.42 ** (1.08, 1.86)			2.32 *** (1.86, 2.90)
Precipitation	0.97 ** (0.95, 1)	0.98 (0.96, 1.01)	1 (0.98, 1.02)	0.99 (0.97, 1.01)
Snow	0.90 ** (0.82, 0.99)	0.82 *** (0.75, 0.89)	0.99 (0.90, 1.08)	0.88 *** (0.80, 0.96)
Daily temperature minimum	1.03 *** (1.02, 1.04)	1.03 *** (1.02, 1.05)	1 (0.99, 1.01)	1.02 *** (1.01, 1.03)
Treatment options (reference: lobectomy)				
Limited resection with adjuvant radiotherapy	0.97 (0.37, 2.52)	0.67 (0.29, 1.54)	1.14 (0.45, 2.88)	0.75 (0.32, 1.72)
Treatment interaction with air pollutants and weather components				
NO_2 × Treatment	1.02 * (1, 1.03)	1.01 *** (1, 1.02)		
SO_2 × Treatment	0.99 (0.93, 1.05)		1.02 (0.97, 1.06)	
CO × Treatment	0.86 (0.60, 1.22)			1.36 *** (1.16, 1.60)
Precipitation × Treatment	1.01 * (1, 1.02)	1 (0.99, 1.01)	1.01 ** (1, 1.02)	1 (0.99, 1)
Snow × Treatment	1.11 ** (1.01, 1.23)	1 (0.93, 1.07)	1.06 (0.97, 1.17)	1.05 (0.97, 1.13)
Temperature minimum × Treatment	1.01 * (1, 1.02)	1 (1, 1.01)	1.01 * (1, 1.01)	1 (1, 1.01)
Race (reference: Black)				
Other	1.01 (0.87, 1.16)	1.03 (0.89, 1.19)	0.98 (0.85, 1.13)	1.02 (0.88, 1.18)
White	0.97 (0.88, 1.07)	0.99 (0.9, 1.09)	0.95 (0.86, 1.05)	0.97 (0.88, 1.07)
Sex (reference: Female)				
Male	1.13 *** (1.06, 1.2)	1.13 *** (1.06, 1.2)	1.11 *** (1.04, 1.18)	1.12 *** (1.05, 1.19)
Tumor Grade (reference: II)				
Grade III	1.10 *** (1.02, 1.19)	1.09 ** (1.01, 1.18)	1.12 *** (1.04, 1.20)	1.10 ** (1.02, 1.18)
Grade IV	1 (0.72, 1.39)	0.97 (0.68, 1.37)	1.02 (0.72, 1.42)	0.95 (0.67, 1.34)
Unknown	0.94 (0.85, 1.06)	0.95 (0.85, 1.06)	0.94 (0.84, 1.04)	0.94 (0.84, 1.04)
Grade I	0.93 ** (0.86, 1.00)	0.93 * (0.86, 1.00)	0.93 * (0.86, 1.00)	0.93 * (0.86, 1.00)

Table 2. *Cont.*

	Multipollutant	NO_2	SO_2	CO
	Hazards of Death Five Years after Diagnosis			
	Duration of Exposure from Five Years before Diagnosis			
Marital status (reference: Divorced)				
Married	0.96 (0.88, 1.06)	0.96 (0.88, 1.06)	0.95 (0.88, 1.06)	0.97 (0.88, 1.06)
Single	0.98 (0.87, 1.10)	0.99 (0.88, 1.11)	0.95 (0.84, 1.07)	0.97 (0.86, 1.09)
Unknown	0.99 (0.85, 1.16)	1 (0.85, 1.16)	0.98 (0.83, 1.14)	0.98 (0.84, 1.14)
Widowed	0.99 (0.88, 1.12)	0.99 (0.88, 1.11)	0.96 (0.86, 1.08)	0.98 (0.87, 1.10)
Tumor size (reference: up to 1 cm)				
>1 cm & ≤2 cm	0.99 (0.89, 1.10)	0.99 (0.89, 1.10)	0.99 (0.89, 1.10)	1 (0.9, 1.11)
>2 cm	1.02 (0.91, 1.15)	1.02 (0.91, 1.14)	1.02 (0.91, 1.13)	1.03 (0.92, 1.15)
Unknown	0.81 (0.45, 1.47)	0.80 (0.45, 1.45)	0.81 (0.46, 1.42)	0.75 (0.41, 1.36)
Tumor histology (reference: squamous cell)				
Adenomas	0.94 (0.88, 1.02)	0.94 (0.87, 1.01)	0.94 (0.87, 1.01)	0.93 * (0.87, 1.01)
Age at diagnosis	1.01 *** (1, 1.01)	1.01 *** (1, 1.01)	1.01 *** (1, 1.01)	1.01 *** (1, 1.01)
Insurance type (reference: Only Medicaid)				
Only Medicare	0.95 (0.82, 1.10)	0.95 (0.82, 1.09)	0.95 (0.83, 1.10)	0.92 (0.80, 1.06)
Only private	0.99 (0.85, 1.14)	0.97 (0.84, 1.12)	1 (0.87, 1.15)	0.95 (0.82, 1.10)
Uninsured	1.35 * (0.98, 1.86)	1.22 (0.89, 1.67)	1.22 (0.89, 1.68)	1.20 (0.87, 1.64)
Unknown	1.11 (0.84, 1.45)	0.99 (0.76, 1.29)	1.11 (0.86, 1.44)	1.02 (0.77, 1.34)
Rural-Urban continuum (reference: Large central metro)				
Large fringe metro	0.99 (0.28, 3.56)	1.24 (0.41, 3.78)	0.62 (0.20, 1.89)	0.95 (0.29, 3.12)
Medium metro	0.09 *** (0.03, 0.27)	0.14 *** (0.05, 0.42)	0.20 *** (0.07, 0.56)	0.20 *** (0.07, 0.58)
Non-metropolitan	1.14 (0.37, 3.53)	1.92 (0.64, 5.82)	0.32 ** (0.11, 0.95)	0.70 (0.24, 2.02)

p-value: * <0.1, ** <0.05, *** <0.01.

4. Discussion

The present study found that patients exposed to higher concentrations of NO_2, SO_2, and CO ambient air pollution before diagnosis had decreased survival after diagnosis. The results from prior similar studies are consistent [3,5,7,30] with the existing study results regarding the estimate direction for air pollutant NO_2 in the presence of weather elements and other prior excluded primary air pollutants, i.e., SO_2 and CO, even though we did not utilize the interpolation or extrapolation techniques supporting the classical and Berkson exposure error theories explained in the exposure assignment section of this paper. It was also determined that snowfall and precipitation decrease mortality after diagnosis, which aligns with the logic that ambient air pollution concentration is lower during precipitation [11,12,14,17–19]. Although our study is the first of its kind, and no

relevant studies exist, other studies examining different health outcomes in the presence of air pollution exposure and survival outcomes in the absence of weather components have been conducted. Our findings align with the existing literature [38,39] and suggest that lobectomy increased surgery-associated morbidity post-lobectomy if exposed to higher levels of air pollutants [29]. Higher levels of ambient air pollutants also affect lung function, as per a recent study, which translates into increased mortality [40].

The present study has several strengths as it utilizes key primary air pollutants such as SO_2 and CO, and weather components such as precipitation, snowfall, and daily minimum temperature to account for the confounding effects. Ozone and the daily maximum temperature pose multicollinearity problems due to their inherent correlation with primary pollutants [16], so they were excluded from the analysis. This exclusion aligns with Eckel et al.'s 2016 study [3], which found that ozone had a non-significant effect on survival outcomes, possibly because of multicollinearity. In addition, the study evaluated the effects of air pollutants and weather components before and after diagnosis to determine their cumulative effects. The CO coefficients were statistically significant. However, the estimates must be interpreted cautiously due to the possibility of residual confounding, exposure measurement errors, and the limited research on the long-term effects of CO in NSCLC. As noted in our study, we did not utilize imputation or interpolation techniques for the missing pollutant data to avoid artificial smoothing; however, this may contribute to larger variances in the derived estimates.

The key limitations of this study include the significant amount of missing data for primary air pollutants, particulate matter (PM), benzene, lead, and wind. For the same reason, we could not determine their interaction with other pollutants, their overall effect on survival outcomes, or their interaction with treatment types. Moreover, the data availability for air pollutant stations within 30 miles, weather stations within 10 miles, and those with less than 33.33% missing values in a month was significantly lower. This led to the use of the most lenient distance and missing percentage model. However, it could be argued that the present results might not change with respect to the hazard rate in the data from the nearest stations, as measurement errors are randomly distributed and not spatially correlated.

Some of the limitations include the insufficient sample size for radiotherapy and limited resection. Therefore, determining the actual hazard rate using these treatment categories is difficult. In addition, the AHRF had significant missing values for area-level information relevant to the study, which could not be controlled for in the analysis. However, the county level and year of diagnosis dummy variables can address these limitations in the time-invariant unobserved variables. In addition, differential yearly analyses, i.e., one, three, and five years before and after diagnosis, might help to estimate any significant time-varying confounders affecting overall estimates. Some of the missing contextual variables that could help reduce estimation bias were the comorbidity score, cardiopulmonary function, lung function, hospital region, patient's overall functional status, occupation, and surgeon expertise. Patient functional status and cardiopulmonary function are variables that seem to be negatively correlated with air pollution and weather exposure. However, they appear to be positively correlated with survival outcomes. In the absence of these variables, the amount of bias is underestimated. The hospital regions seem to be negatively correlated with air pollution and weather exposure, given the greater likelihood of high-volume hospital regions being present in metropolitan areas. The hospital region seems to be positively correlated with survival outcomes, given the higher likelihood of hospitals in metropolitan areas with advanced medical technologies/expertise leading to better survival rates. Estimations of bias that do not include these variables could lead to underestimation. Patient functional status and cardiopulmonary function are other variables that seem to be negatively correlated with air pollution and weather exposure.

However, they appear to be positively correlated with survival outcomes. In the absence of these variables, the derived bias is underestimated. Individuals with higher comorbidity scores might be socioeconomically disadvantaged, as established by prior research, and reside in an underserved area with higher air pollution levels, establishing a positive correlation between air pollutant exposure and comorbidity scores. While comorbidity scores might be negatively correlated with survival outcomes, as established by prior research, higher comorbidity scores impact overall patient quality of life and survival outcomes. In the absence of data on comorbidity scores, the existing hazard coefficient might be underestimated. Similarly, more experienced surgeons tend to reside in urban areas or less polluted areas with a good healthcare infrastructure, and hence are negatively associated with urban–rural categories of patient residence. Surgeon expertise is positively associated with better survival outcomes. Not accounting for this confounder might lead to an underestimation of the hazard ratio. Hence, it was vital to account for key confounders in the present study. For the same reason, our study only measured associational relationships because we did not account for these identified unobserved confounders in the analysis, nor was the study designed to be a randomized control trial or natural experiment. Further, due to data limitations regarding sub-county information, we were not able to completely account for within-county heterogeneity, even after attempting to include fixed county effects, as this study does not account for time-varying confounders.

Moreover, the results of the current study are only generalizable to the population represented by the sub-sample. As most monitors are present in metropolitan areas, potentially due to the higher pollution levels, the results from the present study cannot be generalized to populations in rural areas. The lack of sufficient monitoring stations in non-metropolitan areas necessitates future studies focusing on these areas. The ecological fallacy persists, as county-level exposure values were assigned to individuals. Additionally, the sub-sample lacks a sufficient number of Black individuals, potentially because of their higher presence in non-metropolitan areas. Hence, the study results are only generalizable to white groups.

5. Implications for Practice and Policy

The survival of treated patients with stage 1A NSCLC is negatively associated with increased concentrations of ambient air pollutants such as NO_2, SO_2, and CO, and daily minimum temperature. Hence, it is vital to implement environmental policies that control these emissions or the source of emissions to reduce preventable deaths in stage 1A NSCLC patients with adenocarcinoma or squamous cell carcinoma histology types and other cardiopulmonary patients residing in metropolitan areas. This will not only help improve early-stage lung cancer survival rates but will also help to reduce healthcare cost burdens due to increased air pollution exposure levels and associated reduced lung function or other complications.

Future studies might want to consider particulate matter like PM2.5 and PM10, weather components such as wind, existing primary pollutants, benzene, and lead, and their overall effect on survival outcomes to determine their interaction in a multi-pollutant model, as well as the overall exposure effect on survival outcomes. Kriging or accurate spatiotemporal interpolation could be used to compensate for significant missing exposure values in the data, along with mobility data to determine close-to-true exposure levels. In addition, a similar relationship could be tested using other national cancer registry databases, such as the National Cancer Database, or medical claims data, such as each state Medicare/Medicaid claims data, which provide information on key confounders, such as frailty, treatment timing, hospital region, hospital type, treatment dosage, patient migration status, and overall patient functional status.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of University of Louisville (IRB number 22.0281 on (8 January 2022). The University of Louisville ethics committee approved this study (IRB number 22.0281). The study is exempt according to 45 CFR 46.101(b) under Category 4: Secondary research, for which consent is not required.

Informed Consent Statement: Patient consent was waived as the study is exempt according to 45 CFR 46.101(b) under Category 4: Secondary research, for which consent is not required.

Data Availability Statement: The data that support the findings of this study are available from the authors but restrictions apply to the availability of these data, which were used under license from the NIH National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) plus cancer registry, U.S. Environmental Protection Agency, The Global Historical Climatology Network daily (GHCNd), and Area Health Resource Files for the current study, and so are publicly available upon approved request. Data are, however, available from the authors upon reasonable request and with permission from the NIH NCI SEER plus cancer registry.

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Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A

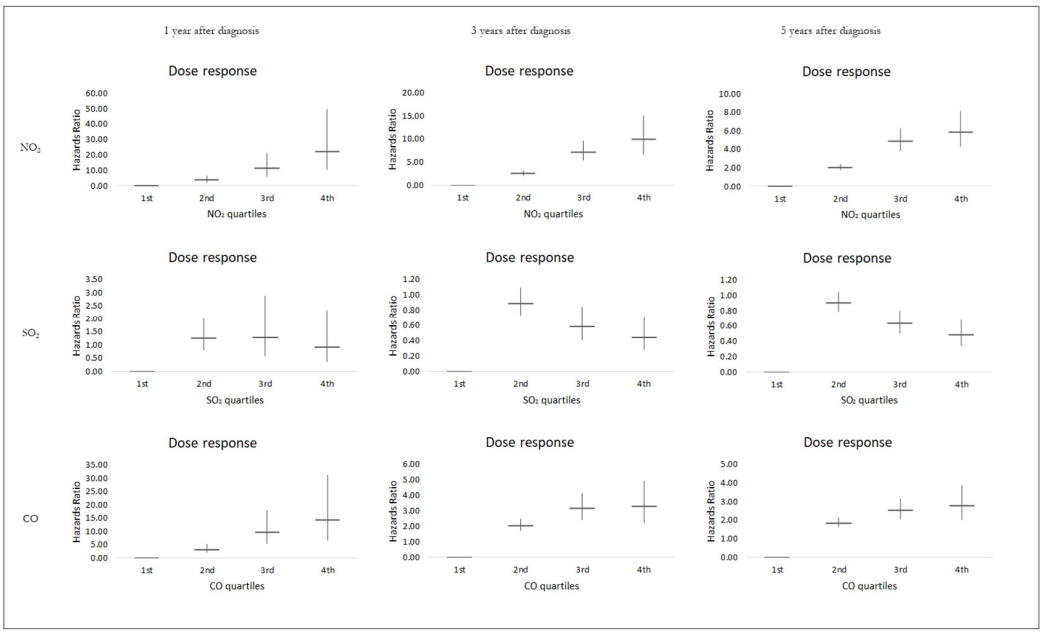


Figure A1. Dose–response relationship for adjusted hazard ratio according to pollutant quartile.

Table A1. (**a**) Frequency statistics of the excluded sample. (**b**) Descriptive statistics of the excluded sample. (**c**) Air pollution and weather monitor stations' distance from the county in miles. (**d**) Data-cleaning steps for air pollutants.

(**a**)

N	**28,509**	
	Frequency	**Percentage**
Tumor Grade		
Grade I	6077	21.32
Grade II	10,769	37.77
Grade III	7917	27.77
Grade IV	152	0.53
Unknown	3594	12.61
Tumor Size		
Up to 1 cm	3135	11
>1 cm and ≤2 cm	8501	29.82
>2 cm	6359	22.31
Unknown size	10,514	36.88
Rural Urban Continuum		
Large central metro	7975	27.97
Large fringe metro	7403	25.97
Medium metro	6442	22.6
Non-metropolitan	6689	23.46
Insurance Type		
Only Medicaid	2913	10.22
Only Medicare	8021	28.13
Only Private	3330	11.68
Uninsured	169	0.59
Unknown	14,076	49.37
Race		
Black	4133	14.5
White	20,755	72.8
Unknown	3621	12.7
Sex		
Female	15,127	53.06
Male	13,382	46.94
Marital Status		
Married	14,404	50.52
Widowed	4807	16.86
Divorced	4483	15.72
Single	2053	7.2
Unknown	2762	9.69
Treatment Guideline Revision Years		
pre 1996	4065	14.26
post 1996	8475	29.73
post 2005	625	2.19
post 2006	768	2.69
post 2007	6298	22.09
post 2010	2473	8.67
post 2012	1142	4.01
post 2013	2662	9.34
post 2015	2000	7.02

(**b**)

N		**28,509**	
	Median	**Mean**	**SD**
Survival months	55	71.2	20.17
Age at diagnosis	66	65.15	9.62

Table A1. *Cont.*

(**c**)

Element monitor	Distance in miles		
	25th Percentile	Median	75th Percentile
Panel A: Sub-sample			
CO	5.57	8.85	12.72
NO_2	6.56	11.66	13.61
SO_2	8.80	15.92	22.22
Precipitation	3.34	3.47	5.40
Snow	3.46	3.757	5.64
Daily minimum temperature	3.37	5.07	7.05
Panel B: Above median			
CO	5.57	10.43	11.48
NO_2	6.56	11.66	11.77
SO_2	8.80	15.31	15.92
Precipitation	3.34	3.45	4.22
Snow	3.46	3.55	5.23
Daily minimum temperature	3.50	6.20	7.05
Panel C: Below median			
CO	6.85	8.85	17.20
NO_2	6.56	11.15	15.13
SO_2	11.35	16.60	22.92
Precipitation	2.53	3.58	6.61
Snow	2.60	3.95	6.54
Daily minimum temperature	2.54	4.19	6.93

(**d**)

Steps	Description
1	(1) Rename, and clean raw files by generating date, day, year and month variables. (2) Keeping only one sample duration, and observations with non-zero latitude and longitude values (3) Generating unique siteID's by grouping corresponding latitude and longitude (4) Generating a variable for site monitors which allots unique site monitor, a unique day number for poc numbers (5) Generating a variable for site monitors which allots same number to different poc's per unique siteID with same day observation (6) Excluding observations with excluded even type (7) For a unique siteID only one observation is present as we keep only one poc per unique siteID
2	(1) Renaming and cleaning pollutant/weather data files to prep for merging (2) Assigning 3 nearest pollutant station monitor to the county centroid (3) Merging 1-3 nearest site values into one file
3	(1) Drop weather and AHRF variables (2) Generate 10-40 miles stations from country centroid with corresponding arithmetic mean pollutant values (3) Generating monthly values from daily values. Calculating percentage missing, for each mile: 50% , 33.33%, 25%, and 20% (4) For each mile and each % missing four monthly measures are calculated: mean, median, max and iqr (5) Collapsing all miles, all % missing, and all measures to assign corresponding only one value per month per FIPS
4	Appending all years, all pollutants files into one and assigning
5	Merging Air pollution with Weather files
6	After renaming variables the file is reshaped into wide format from long to achieve only one FIPS per row. The Air pollutant variables are separated from merged file to generate reshaped file and save separately for each pollutant each mile, each element, each %.

Table A2. Mortality five years after diagnosis, according to the annual average of monthly median values.

	Multipollutant			**NO_2**			**SO_2**			**CO**		
	Mortality Five Years Exposure Levels at Measured Timepoints Pre-/Post-Diagnosis											
	1 yr bf	**3 yrs bf**	**5 yrs bf**	**1 yr bf**	**3 yrs bf**	**5 yrs bf**	**1 yr bf**	**3 yrs bf**	**5 yrs bf**	**1 yr bf**	**3 yrs bf**	**5 yrs bf**
Air pollutants and weather elements												
NO_2	1.04 *** (1.02, 1.06)	1.05 *** (1.03, 1.08)	1.08 *** (1.06, 1.11)	1.05 *** (1.03, 1.62)	1.07 *** (1.05, 1.81)	1.10 *** (1.08, 8.09)						
SO_2	1.18 *** (1.12, 1.23)	1.19 *** (1.14, 1.24)	1.19 *** (1.14, 1.24)				1.17 *** (1.12, 1.23)	1.18 *** (1.13, 1.23)	1.17 *** (1.12, 1.22)			
CO	1.39 *** (1.09, 1.78)	1.41 *** (1.10, 1.81)	1.52 *** (1.17, 1.96)							1.73 *** (1.39, 2.14)	1.89 *** (1.51, 2.36)	2.27 *** (1.81, 2.85)
Precipitation	1.01 (0.94, 1.09)	1 (0.91, 1.10)	1.08 (0.97, 1.20)	0.96 (0.89, 1.04)	0.93 (0.84, 1.03)	0.98 (0.89, 1.09)	1.02 (0.95, 1.10)	1.02 (0.93, 1.12)	1.09 * (0.99, 1.21)	0.97 (0.90, 1.04)	0.93 (0.84, 1.02)	0.98 (0.89, 1.09)
Snow	0.76 (0.16, 3.64)	0.28 (0.06, 1.34)	0.05 *** (0.01, 0.33)	0.45 (0.10, 1.94)	0.29 (0.06, 1.30)	0.09 *** (0.02, 0.50)	1.24 (0.30, 5.07)	0.80 (0.18, 3.60)	0.44 (0.08, 2.31)	1.02 (0.24, 4.31)	0.38 (0.08, 1.80)	0.09 *** (0.02, 0.54)
Daily temperature minimum	1.01 (1.00, 1.02)	1.01 ** (1.00, 1.02)	1.03 *** (1.02, 1.04)	1.01 (1.00, 1.02)	1.01 ** (1.00, 1.02)	1.03 *** (1.02, 1.04)	0.99 ** (0.98, 1.00)	0.99 *** (0.98, 0.99)	0.99 * (0.98, 1.00)	1 (1.00, 1.01)	1.01 (1.00, 1.02)	1.02 *** (1.01, 1.03)
Treatment options (reference: lobectomy)												
Limited resection with adjuvant radiotherapy	1.01 (0.64, 1.59)	0.99 (0.62, 1.59)	1.01 (0.62, 1.64)	0.74 (0.49, 1.13)	0.71 (0.47, 1.09)	0.75 (0.49, 1.13)	1.36 (0.89, 2.07)	1.32 (0.85, 2.06)	1.25 (0.79, 1.98)	0.99 (0.60, 1.36)	0.85 (0.57, 1.28)	0.84 (0.56, 1.26)
Treatment interaction with air pollutant and weather elements												
NO_2 × Treatment	1.02 (1.00, 1.04)	1.02 ** (1.00, 1.04)	1.02 * (1.00, 1.03)	1.02 *** (1.01, 1.03)	1.02 *** (1.01, 1.03)	1.01 *** (1.01, 1.02)						
SO_2 × Treatment	0.95 (0.88, 1.02)	0.95 (0.89, 1.02)	0.96 (0.90, 1.03)				0.98 (0.91, 1.05)	0.98 (0.91, 1.05)	0.98 (0.92, 1.05)			
CO × Treatment	0.99 (0.70, 1.41)	1.01 (0.71, 1.44)	1.01 (0.71, 1.43)							1.32 *** (1.07, 1.63)	1.31 *** (1.07, 1.61)	1.29 *** (1.07, 1.56)
Precipitation × Treatment	0.93 (0.81, 1.07)	0.94 (0.84, 1.05)	0.94 (0.84, 1.05)	0.92 (0.80, 1.06)	0.93 (0.83, 1.04)	0.93 (0.83, 1.04)	0.94 (0.82, 1.07)	0.94 (0.84, 1.05)	0.95 (0.85, 1.06)	0.91 (0.79, 1.05)	0.93 (0.83, 1.03)	0.92 (0.82, 1.03)
Snow × Treatment	0.84 (0.15, 4.76)	1.04 (0.18, 5.89)	1.03 (0.15, 6.96)	1.12 (0.20, 6.26)	1.32 (0.22, 8.02)	1.27 (0.18, 9.03)	0.64 (0.12, 3.50)	0.65 (0.12, 3.55)	0.67 (0.10, 4.23)	1.11 (0.21, 5.84)	1.34 (0.24, 7.60)	1.51 (0.23, 9.93)
Temperature minimum × Treatment	1 (0.99, 1.00)	1 (0.99, 1.00)	1 (0.99, 1.00)	1 (1.00, 1.00)	1 (1.00, 1.00)	1 (1.00, 1.01)	1 (0.99, 1.00)	1 (0.99, 1.00)	1 (0.99, 1.00)	1 (0.99, 1.00)	1 (1.00, 1.00)	1 (1.00, 1.01)

p-value: * <0.01, ** <0.05, *** <0.10.

Table A3. Mortality five years after diagnosis according to annual average of monthly maximum values.

	Multipollutant			**NO_2**			**SO_2**			**CO**		
	Mortality Five Years Exposure Levels at Measured Timepoints Pre-/Post-Diagnosis											
	1 yr bf	**3 yrs bf**	**5 yrs bf**	**1 yr bf**	**3 yrs bf**	**5 yrs bf**	**1 yr bf**	**3 yrs bf**	**5 yrs bf**	**1 yr bf**	**3 yrs bf**	**5 yrs bf**
Air pollutants and weather elements												
NO_2	1.02 *** (1.01, 1.04)	1.02 *** (1.01, 1.04)	1.02 *** (1.01, 1.04)	1.04 *** (1.03, 1.50)	1.05 *** (1.04, 1.72)	1.05 *** (1.04, 2.35)						
SO_2	1.04 *** (1.02, 1.05)	1.04 *** (1.02, 1.05)	1.04 *** (1.03, 1.05)				1.04 *** (1.02, 1.05)	1.04 *** (1.03, 1.05)	1.04 *** (1.03, 1.05)			
CO	1.55 *** (1.34, 1.79)	1.61 *** (1.36, 1.90)	1.64 *** (1.36, 1.98)	1 *** (1, 1)	1 *** (1, 1)	1 * (1, 1)				1.79 *** (1.58, 2.04)	1.97 *** (1.72, 2.24)	2.05 *** (1.80, 2.33)
Precipitation	1 *** (1, 1)	1 *** (1, 1)	1 *** (1, 1)	1.00 (1, 1)	0.99 ** (1, 1)	0.99 ** (1, 1)	1.00 (1, 1)	1.00 (1, 1)	1.00 (1, 1)	1 *** (1, 1)	1 *** (1, 1)	1 *** (1, 1)
Snow	1.00 (0.99, 1.00)	0.99 ** (0.99, 1.00)	0.99 ** (0.98, 1.00)	1.01 *** (1.00, 1.01)	1.01 *** (1.00, 1.02)	1.02 *** (1.01, 1.03)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	0.99 (0.99, 1.00)	1.00 (0.99, 1.00)	0.99 (0.99, 1.00)	0.99 ** (0.98, 1.00)
Daily temperature minimum	1.01 *** (1.00, 1.02)	1.01 *** (1.01, 1.02)	1.02 *** (1.01, 1.03)	1 *** (1, 1)	1 *** (1, 1)	1 * (1, 1)	1.00 (0.99, 1.00)	1.00 (0.99, 1.01)	1.01 (1.00, 1.02)	1.01 *** (1.00, 1.02)	1.01 *** (1.01, 1.02)	1.02 *** (1.01, 1.03)
Treatment options (reference: lobectomy)												
Limited resection with adjuvant radiotherapy	1.40 (0.50, 3.88)	1.07 (0.35, 3.26)	1.11 (0.35, 3.51)	0.94 (0.36, 2.43)	0.73 (0.27, 2.00)	0.76 (0.28, 2.10)	1.69 (0.57, 5.04)	1.08 (0.35, 3.31)	0.89 (0.29, 2.75)	1.14 (0.42, 3.10)	0.85 (0.30, 2.38)	0.77 (0.28, 2.16)
Treatment interaction with air pollutant and weather elements												
NO_2 × Treatment	1.02 (1.01, 1.04)	1.02 *** (1.01, 1.04)	1.02 *** (1.01, 1.03)	1.01 *** (1.01, 1.02)	1.01 *** (1.01, 1.02)	1.01 *** (1.01, 1.02)						
SO_2 × Treatment	0.99 (0.97, 1.00)	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)				1 (0.98, 1.01)	1 (0.98, 1.02)	1 (0.99, 1.02)			
CO × Treatment	0.85 (0.68, 1.07)	0.85 (0.69, 1.06)	0.86 (0.69, 1.06)							1.16 ** (1.03, 1.32)	1.16 ** (1.03, 1.30)	1.15 *** (1.03, 1.28)
Precipitation × Treatment	1 (1, 1)	1 (1, 1)	1 (1, 1)	1 (1, 1)	1 (1, 1)	1 (1, 1)	1 (1, 1)	1 (1, 1)	1 (1, 1)	1 (1, 1)	1 (1, 1)	1 (1, 1)
Snow × Treatment	1 (0.99, 1.00)	1 (0.99, 1.00)	1 (0.99, 1.00)	1 (0.99, 1.00)	1 (0.99, 1.00)	1 (0.99, 1.00)	1 (0.99, 1.00)	1 (0.99, 1.00)	1 (0.99, 1.00)	1 (0.99, 1.01)	1 (0.99, 1.01)	1 (0.99, 1.01)
Temperature minimum × Treatment	0.99* (0.98, 1.00)	0.99 (0.99, 1.00)	0.99 (0.98, 1.00)	1 (0.99, 1.00)	1 (0.99, 1.01)	1 (0.99, 1.01)	0.99 (0.99, 1.00)	1 (0.99, 1.01)	1 (0.99, 1.01)	1 (0.99, 1.00)	1 (0.99, 1.01)	1 (0.99, 1.01)

p-value: * <0.01, ** <0.05, *** <0.10.

Table A4. Mortality five years after diagnosis, along with air pollution, weather, treatment type and study covariates according to annual monthly mean.

	Multipollutant		**NO_2**		**SO_2**		**CO**	
	Mortality Five Years Exposure Levels at Measured Timepoints Pre-/Post-Diagnosis							
	1 yr bf	**3 yrs. bf**	**1 yr bf**	**3 yrs. bf**	**1 yr bf**	**3 yrs. bf**	**1 yr bf**	**3 yrs. bf**
Air pollutants and weather components								
NO_2	1.04 *** (1.02, 1.06)	1.06 *** (1.04, 1.08)	1.06 *** (1.04, 1.29)	1.08 *** (1.06, 1.68)				
SO_2	1.16 *** (1.12, 1.21)	1.17 *** (1.13, 1.22)			1.15 *** (1.11, 1.20)	1.16 *** (1.12, 1.21)		
CO	1.53 *** (1.19, 1.97)	1.51 *** (1.16, 1.96)					1.90 *** (1.52, 2.38)	2.07 *** (1.65, 2.60)
Precipitation	0.98 ** (0.97, 1)	0.97 *** (0.95, 0.99)	0.98 ** (0.97, 1)	0.98 *** (0.96, 0.99)	1 (0.98, 1.01)	1 (0.98, 1.01)	0.99 * (0.97, 1)	0.98 ** (0.96, 1)
Snow	0.99 (0.92, 1.07)	0.96 (0.88, 1.05)	0.94 (0.87, 1.01)	0.88 *** (0.81, 0.96)	1 (0.93, 1.08)	1.01 (0.93, 1.10)	1 (0.93, 1.07)	0.94 (0.87, 1.03)
Daily temperature minimum	1.01 (1, 1.02)	1.01 ** (1, 1.02)	1.01 (1, 1.01)	1.01 ** (1, 1.02)	0.99 ** (0.99, 1)	0.99 ** (0.98, 1)	1.01 (1, 1.01)	1.01 (1, 1.02)
Treatment options (reference: lobectomy)								
Daily temperature minimum	1.01 (1, 1.02)	1.01 ** (1, 1.02)	1.01 (1, 1.01)	1.01 ** (1, 1.02)	0.99 ** (0.99, 1)	0.99 ** (0.98, 1)	1.01 (1, 1.01)	1.01 (1, 1.02)
Treatment interaction with air pollutants and weather components								
NO_2 × Treatment	1.01 (1, 1.03)	1.02 * (1, 1.03)	1.01 * (1, 1.02)	1.01 * (1, 1.02)				
SO_2 × Treatment	0.99 (0.93, 1.04)	0.98 (0.93, 1.04)			1.02 (0.97, 1.07)	1.02 (0.98, 1.07)		
CO × Treatment	0.94 (0.68, 1.29)	0.85 (0.60, 1.21)					1.16 (0.95, 1.43)	1.24 ** (1.04, 1.48)
Precipitation × Treatment	1 (0.99, 1.01)	1.01 (1, 1.02)	1 (0.99, 1)	1 (0.99, 1.01)	1 (1, 1.01)	1.01 * (1, 1.02)	1 (0.99, 1.01)	1 (0.99, 1.01)
Snow × Treatment	1.10 ** (1, 1.20)	1.14 *** (1.03, 1.25)	1.03 (0.96, 1.10)	1.04 (0.97, 1.12)	1.09 ** (1, 1.18)	1.10 ** (1, 1.20)	1.03 (0.95, 1.12)	1.06 (0.98, 1.14)
Temperature minimum × Treatment	1 (1, 1.01)	1.01 * (1, 1.02)	1 (1, 1.01)	1 (1, 1.01)	1.01 ** (1, 1.01)	1.01 ** (1, 1.01)	1 (1, 1.01)	1 (1, 1.01)
Race (reference: Black)								
Other	1 (0.87, 1.16)	1 (0.86, 1.15)	1.02 (0.88, 1.18)	1.02 (0.88, 1.18)	0.99 (0.86, 1.14)	0.98 (0.85, 1.13)	1.02 (0.88, 1.17)	1.01 (0.88, 1.17)
White	0.97 (0.88, 1.07)	0.96 (0.88, 1.06)	0.98 (0.89, 1.08)	0.98 (0.89, 1.08)	0.96 (0.87, 1.06)	0.95 (0.87, 1.05)	0.97 (0.88, 1.07)	0.97 (0.88, 1.07)

Table A4. *Cont.*

	Multipollutant		NO_2		SO_2		CO	
	Mortality Five Years Exposure Levels at Measured Timepoints Pre-/Post-Diagnosis							
	1 yr bf	**3 yrs. bf**	**1 yr bf**	**3 yrs. bf**	**1 yr bf**	**3 yrs. bf**	**1 yr bf**	**3 yrs. bf**
Sex (reference: Female)								
Male	1.12 *** (1.05, 1.19)	1.12 *** (1.05, 1.19)	1.12 *** (1.05, 1.19)	1.12 *** (1.06, 1.19)	1.11 *** (1.04, 1.17)	1.11 *** (1.04, 1.18)	1.12 *** (1.05, 1.19)	1.12 *** (1.05, 1.19)
Tumor Grade (reference: II)								
Grade III	1.10 *** (1.02, 1.19)	1.10 *** (1.02, 1.19)	1.09 ** (1.01, 1.18)	1.09 ** (1.01, 1.17)	1.12 *** (1.04, 1.20)	1.12 *** (1.04, 1.20)	1.09 ** (1.01, 1.18)	1.09 ** (1.02, 1.18)
Grade IV	1 (0.72, 1.39)	0.99 (0.71, 1.37)	0.98 (0.70, 1.38)	0.97 (0.69, 1.36)	1.01 (0.72, 1.41)	1.01 (0.72, 1.42)	0.96 (0.68, 1.37)	0.95 (0.67, 1.35)
Unknown	0.95 (0.85, 1.06)	0.94 (0.85, 1.05)	0.95 (0.85, 1.06)	0.95 (0.85, 1.06)	0.94 (0.84, 1.05)	0.94 (0.84, 1.05)	0.94 (0.85, 1.05)	0.94 (0.84, 1.05)
Grade I	0.92 ** (0.85, 1)	0.92 ** (0.86, 1)	0.93 * (0.86, 1)	0.93 * (0.86, 1)	0.92 ** (0.86, 1)	0.93 ** (0.86, 1)	0.93 * (0.86, 1)	0.93 * (0.86, 1)
Marital status (reference: Divorced)								
Married	0.96 (0.88, 1.05)	0.96 (0.88, 1.06)	0.96 (0.88, 1.05)	0.96 (0.88, 1.06)	0.95 (0.86, 1.04)	0.95 (0.86, 1.04)	0.96 (0.88, 1.05)	0.96 (0.88, 1.06)
Single	0.98 (0.87, 1.10)	0.98 (0.87, 1.10)	0.98 (0.87, 1.10)	0.98 (0.87, 1.11)	0.96 (0.85, 1.08)	0.95 (0.85, 1.07)	0.96 (0.85, 1.08)	0.97 (0.86, 1.09)
Unknown	0.98 (0.84, 1.15)	0.99 (0.85, 1.16)	0.99 (0.84, 1.16)	1 (0.85, 1.16)	0.98 (0.84, 1.15)	0.98 (0.83, 1.15)	0.97 (0.83, 1.14)	0.98 (0.84, 1.14)
Widowed	0.98 (0.87, 1.10)	0.98 (0.88, 1.11)	0.98 (0.88, 1.11)	0.99 (0.88, 1.11)	0.96 (0.85, 1.08)	0.96 (0.85, 1.08)	0.97 (0.87, 1.09)	0.98 (0.87, 1.10)
Tumor size (reference: up to 1 cm)								
>1 cm & ≤2 cm	0.99 (0.89, 1.10)	0.99 (0.89, 1.10)	1 (0.90, 1.11)	1 (0.90, 1.11)	0.99 (0.90, 1.10)	0.99 (0.89, 1.09)	1.01 (0.91, 1.12)	1.01 (0.91, 1.12)
>2 cm	1.02 (0.91, 1.14)	1.02 (0.91, 1.14)	1.02 (0.91, 1.14)	1.02 (0.91, 1.14)	1.02 (0.91, 1.14)	1.01 (0.91, 1.13)	1.03 (0.92, 1.15)	1.02 (0.92, 1.15)
Unknown	0.87 (0.49, 1.55)	0.85 (0.47, 1.57)	0.88 (0.49, 1.56)	0.86 (0.47, 1.57)	0.84 (0.48, 1.47)	0.82 (0.47, 1.44)	0.76 (0.42, 1.38)	0.75 (0.41, 1.39)

Table A4. *Cont.*

	Multipollutant		NO_2		SO_2		CO	
	Mortality Five Years Exposure Levels at Measured Timepoints Pre-/Post-Diagnosis							
	1 yr bf	**3 yrs. bf**	**1 yr bf**	**3 yrs. bf**	**1 yr bf**	**3 yrs. bf**	**1 yr bf**	**3 yrs. bf**
Tumor histology (reference: squamous cell)								
Adenomas	0.94 (0.87, 1.01)	0.95 (0.88, 1.02)	0.94 * (0.87, 1.01)	0.94 (0.87, 1.01)	0.94 * (0.87, 1.01)	0.94 (0.87, 1.01)	0.93 * (0.87, 1.01)	0.93 * (0.87, 1.01)
Age at diagnosis	1.01 *** (1, 1.01)	1.01 *** (1, 1.01)	1.01 *** (1, 1.01)	1.01 *** (1, 1.01)	1.01 *** (1, 1.01)	1.01 *** (1, 1.01)	1.01 *** (1, 1.01)	1.01 *** (1, 1.01)
Insurance type (reference: Only Medicaid)								
Only Medicare	0.93 (0.81, 1.07)	0.93 (0.81, 1.08)	0.94 (0.82, 1.08)	0.94 (0.82, 1.08)	0.94 (0.82, 1.09)	0.94 (0.82, 1.09)	0.92 (0.80, 1.06)	0.92 (0.79, 1.06)
Only private	0.97 (0.84, 1.12)	0.97 (0.84, 1.12)	0.97 (0.84, 1.11)	0.96 (0.84, 1.11)	1 (0.87, 1.15)	0.99 (0.86, 1.14)	0.95 (0.82, 1.09)	0.94 (0.82, 1.09)
Uninsured	1.27 (0.92, 1.76)	1.31 * (0.95, 1.81)	1.17 (0.85, 1.61)	1.19 (0.87, 1.64)	1.22 (0.89, 1.68)	1.23 (0.90, 1.69)	1.15 (0.83, 1.58)	1.17 (0.86, 1.61)
Unknown	1.05 (0.80, 1.37)	1.07 (0.82, 1.40)	0.93 (0.71, 1.21)	0.96 (0.73, 1.25)	1.07 (0.83, 1.39)	1.09 (0.84, 1.41)	0.98 (0.74, 1.28)	0.98 (0.75, 1.29)
Rural-Urban continuum (reference: Large central metro)								
Large fringe metro	0.84 (0.26, 2.67)	0.93 (0.28, 3.12)	0.98 (0.34, 2.84)	1.16 (0.40, 3.38)	0.57 (0.19, 1.72)	0.55 (0.18, 1.66)	0.86 (0.29, 2.58)	0.91 (0.30, 2.80)
Medium metro	0.10 *** (0.04, 0.27)	0.07 *** (0.03, 0.20)	0.11 *** (0.04, 0.30)	0.10 *** (0.03, 0.28)	0.16 *** (0.06, 0.40)	0.15 *** (0.06, 0.40)	0.12 *** (0.05, 0.31)	0.12 *** (0.05, 0.34)
Non-metropolitan	0.45 * (0.18, 1.10)	0.46 (0.17, 1.21)	0.53 (0.21, 1.29)	0.64 (0.24, 1.68)	0.23 *** (0.10, 0.56)	0.24 *** (0.09, 0.61)	0.37 ** (0.15, 0.87)	0.36 ** (0.14, 0.91)

p-value: * <0.01, ** <0.05, *** <0.10.

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