How Chronologic Age Modifies the Effect of Lung Cancer on Short-term Survival Following Hospitalization

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Abstract:

Lung cancer has been one of the leading causes of death in the United States, with the five-year survival of non-small cell lung cancer (NSCLC) reported to be 19% and of small-cell lung cancer to be only 6%. Once reaching the advanced stages of lung cancer (Stage III and Stage IV), patients’ short-term survival rate declines rapidly. Many studies have investigated the individual effect of chronologic age and lung cancer on patients’ short-term survival outcomes. Nonetheless, very few studies have investigated how chronologic age could modify the effect of lung cancer on short-term survival. There are also established studies that investigated the association of advanced-stage cancers and survival outcomes in different age groups, yet they did not look at lung cancer specifically. Therefore, the objective of this study was to evaluate whether the effect of lung cancer on short-term survival was modified by chronologic age, measured on both multiplicative and additive scales. This study was a secondary analysis using data from the SUPPORT study by Knaus, et al. in 1995, with the original purpose of developing and validating a prognostic model predicting individual’s survival probability. The study population included 9105 patients from five tertiary care centers who were diagnosed during the first 24 hours after study entry and classified into one of the nine disease groups: nontraumatic coma, multiple organ system failure and malignancy, acute respiratory failure, multiple organ system failure and sepsis, acute exacerbation of severe chronic obstructive pulmonary disease, acute exacerbation of severe congestive heart failure, chronic liver disease, colon cancer with liver metastasis, and non-small cell carcinoma of the lung (NSCLC) (Knaus et al, 1995). All patients were predicted to have overall 6-month survival rates of 50% according to a literature review (Knaus et al, 1995). In this study, patients were classified according to their lung cancer diagnoses and age groups. In stratified analyses, lung cancer was associated with an 110%, 58%
and 35% increase in short-term death among the youngest, middle and oldest age groups, respectively, compared with patients without lung cancer. The stratum-specific estimates were significantly different from each other. The second analysis comparing the observed and expected joint effects of age and lung cancer indicated that there was effect modification of lung cancer across strata of age on both additive and multiplicative scales, and the interaction between two factors tended to be antagonistic. More specifically, for the multiplicative scale interaction, the p-values for the cross-product terms between age tertiles and lung cancer diagnoses were highly significant (p<0.0001). The ratio of the RRrs were 0.59 (95% CI: 0.49, 0.62). The Relative Excess Risk due to Interaction (RERI) was -0.73 (95% CI: -0.62, -0.80), and the p-value for the RERI was 0.0014. That is, despite advanced-stage NSCLC being associated with an elevated risk of short-term death, this risk became less apparent in the older population. These results should influence policy by assuring that age is used appropriately in lung cancer treatment guidelines and medical decision making.
Introduction:

Despite all efforts at management, lung cancer remains a critical health problem in the United States. According to the American Cancer Society (2019), the number of new cases of lung cancer in 2020 is estimated to be 228,820, representing 15% of the new cases of cancer. Lung cancer is usually divided into two general types: non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). NSCLC accounts for 85% of lung cancer in males and females, and usually is located in the lungs or nearby lymph nodes, with more advanced stages increasing the possibility that the cancer cells spread to fluid in the area around the lungs and/or to other organs (Hassan et al, 2016). SCLC, accounting for the remaining 15% of lung cancer, tend to grow significantly more quickly than NSCLC, and the rate of metastasis is nearly three times the rate for NSCLC (Hassan et al, 2016).

In the early stage of NSCLC (Stage 0, I and II), where the cancers have only invaded limited part of one side of the lungs, there are only minor to moderate symptoms of coughing, difficulty of breathing, fatigue, and hoarseness (Walter et al, 2015). Symptoms only progress to bone pain, swelling in the face and limbs, headache and even jaundice when the cancers start developing to the advanced stages (Stage III and IV) (Walter et al, 2015). SCLC, unfortunately, is mostly asymptomatic. When symptoms such as shortness of breath, wheezing, fever, and persistent coughing with blood in mucus appear, they usually indicate that the cancers have invaded both lungs, lymph tissues around the lungs, and other body organs (Walter et al, 2015). Common tests for NSCLC and SCLC involve imaging tests. An X-ray image of lungs may reveal an abnormal mass or nodule. A CT scan can reveal small lesions in lungs that might not be detected on an X-
ray (Cruz et al, 2013). For lung cancers in more advanced stages, sputum cytology usually reveals the presence of lung cancer cells by looking at the sputum produced by cough, under the microscope (Cruz et al, 2013).

The prognosis for lung cancer remains poor. Since the early stage of lung cancer usually does not show symptoms, up to 85% of patients are diagnosed at an advanced stage. In the U.S., the five-year survival rate for all people with all types of lung cancer is only estimated to be 19%. The 5-year survival rate for NSCLC is 23%, compared to 6% for small cell lung cancer (American Cancer Society, 2019). The early stages of NSCLC and SCLC can be usually removed by surgery, with no chemotherapy or radiotherapy needed (Cruz et al, 2013). Patients who are healthy enough for surgery can be treated by lobectomy, which only takes out the tumor tissues, or by segmentectomy, that only removes the tumor affected area of the lung (Cruz et al, 2013).

Nonetheless, advanced stage NSCLC and SCLC can often only be treated by non-surgical treatments. Non-surgical treatment options, including chemotherapy, radiotherapy, or targeted therapy, have been investigated to determine whether they prolong the overall survival of patients with advanced lung cancer (Ranman et al, 2018). Chemotherapy usually involves intake of medications that are designed to destroy fast-growing, cancer cells. The medications, depending on types and dosages, can be taken orally or by injection (Ranman et al, 2018). Because chemotherapy drugs travel through the body, they also impact and kill healthy, fast-growing cells. Blood-forming cells, hair follicles, and cells in mouth, digestive and reproductive tracts are usually affected by chemotherapy medications (Ranman et al, 2018). Therefore, lots of patients undergoing chemotherapy suffer from moderate to severe side effects, including anemia, bruising, temporary hair loss, nausea, constipation and diarrhea (Ranman et al, 2018).
Radiotherapy is usually delivered externally, through external beam radiation, targeting the
tumor cells to destroy or damage them. Side effects of radiotherapy appear to be more tolerable
and less frequent than chemotherapy, depending on the type and stage of cancers (Ranman et al,
2018). Patients who undertake regular radiotherapy usually still experience some degree of dry
mouth, difficult swallowing, nausea and hair loss (Ranman et al, 2018).

Due to the unpleasant side effects and limited progress associated with chemotherapeutics,
studies have started to investigate whether subgroups of patients may be identified to determine
who would benefit most from specific treatment strategies (Kim et al, 2020). For example, there
has been a promising field of developing personalized medicine and precision medicine (PPM),
that incorporate one person’s genomic data, lifestyle and socio-economic status together with her
cancer diagnosis, to design the best course of treatment options for this individual (Davidoff et
al, 2019). This may lead to improvement in the selection of patients with poor prognosis to be
treated only with palliative care, which may preserve the quality of life for patients and relieve
the burden of adverse events and complications brought by systematic chemotherapy (Jemal et
al, 2010). On the other hand, there were also studies showing that some group of patients might
have been consistently undertreated: one study by Koppert et al (2012) found that older patients
(>=75 years) are less likely to be offered standard lung cancer treatment, due to concern
regarding their intolerance of treatments and physiologic burden exerted by side effects (Koppert
et al, 2012). Physicians tend not to display the complete option sets of treatments to those older
patients and to their families with full explanations or discussion with regard to these treatment.
(Koppert et al, 2012).

Several critical prognosis factors have been shown to be predictive of lung cancer survival.
Good prognosis factors include early disease at diagnosis, no significant weight loss (not >5%),
normal range of physiologic variables, (e.g., blood oxygen level, mean blood pressure, and heart rate) and female gender (Lett et al, 2013). The study also suggested that race, ethnicity, education and income level play important roles in lung cancer development. Lower education and income disproportionately came from social inequality, resulting in higher chances of cigarette smoking, alcohol assumption, along with exposure to other risk factors (Lett et al, 2013). Biologically, lung cancer was shown to be significantly related to mutation of the tumor suppressor, gene p53, the activation of proto-oncogene K-ras and inactivation of another biological marker, Transcription Terminator Factor I (TTFI), which lead to uncontrolled DNA and cell replication (Lett et al, 2013). Among all identified prognosis factors, age has been investigated extensively as a negative prognosis factor for survival outcome in advanced-stage lung cancer patients (Venuta et al, 2016). Aging is associated with less effective DNA repair mechanism to keep cell mutation on check, and with cumulative exposure to more carcinogens (Venuta et al, 2016).

Many studies have investigated the individual impact of age and of having advanced-stage lung cancer on the short-term survival outcomes, yet only a few of the studies evaluated how age could potentially modify the effect of advanced-stage lung cancer on short-term survival. The Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT) showed as one of their findings that although chronologic age had independent prognostic value for all severely ill, hospitalized patients with extremely poor prognoses, the incremental influence of age on short-term survival for cancer patients was small (Knaus et al, 1995). Another study by Lu et al. has shown that after adjusting for clinicopathologic factors, even though age was inversely associated with cancer survival among patients with advanced-
stage cancers, this inverse association was significantly weaker in patients older than 70 years, compared with younger patients.

Importantly, all of the studies mentioned above either did not adjust for critical covariates in their final models or they did not investigate or quantify the interaction effect of age with lung cancer diagnosis. Therefore, this study aimed to evaluate how chronologic age modifies the impact of lung cancer on short-term (180 days) survival outcome for severely ill, hospitalized patients from the patient population selected into the SUPPORT study. 9105 patients were divided into “lung cancer” vs. “not-lung cancer” patients based on their initial diagnoses during the first 24 hours of study entry. The binary survival outcomes, “alive” or “death”, were obtained at the end of the study period. Patients’ ages were divided into tertiles and stratified when analyzing the results. Multivariable Poisson regression with robust standard errors were used to analyze whether the effect of lung cancer on short-term survival was modified by age, adjusting for potential confounders. The presence and direction of effect modification of age on advanced-stage lung cancer, on both multiplicative and additive scales, were evaluated.
Methods

Patient Selection

The study population consisted of 9105 patients participating in the SUPPORT study from 1989 to 1995. A literature review identified nine diagnostic groups that had sufficient prognostic information from the medical record to be included (Knaus et al, 1995). All patients from participating tertiary care centers in the United States (described below) who had at least one of nine illnesses, met the severity criteria, and who were expected to have an overall 6-month mortality rate of 50% were selected into the SUPPORT study (Knaus et al, 1995). Patients were diagnosed during the first 24 hours after study entry, and classified into one of the following nine disease groups: nontraumatic coma, multiple organ system failure and malignancy, acute respiratory failure, multiple organ system failure and sepsis, acute exacerbation of severe chronic obstructive pulmonary disease, acute exacerbation of severe congestive heart failure, chronic liver disease, colon cancer with liver metastasis, and non-small cell carcinoma of the lung (NSCLC) (Knaus et al, 1995). In addition, patients had to be more than 18 years of age and were excluded if they 1) died within 48 hours of hospitalization, 2) were scheduled to be discharged within 72 hours of admission, 3) had acquired immunodeficiency syndrome, 4) were admitted with head trauma, 5) were pregnant, 6) had trauma other than acute respiratory failure or multiple organ system failure, 7) had acute burns, 8) were admitted to the psychiatric unit, or 9) did not speak English (Knaus et al, 1995). For the purpose of this study, patients who were younger than 20 years old and older than 80 years old were also excluded, as there were no patients younger than 20 years old who had lung cancer, and no patients older than 80 years old who died of lung cancer. Detailed inclusion and exclusion criteria are included in Appendix I.
Data Collection

The SUPPORT study was conducted in two phases. Phase I data were collected from June 1989 to 1991, and Phase II data were collected from January 1992 to January 1994. Patients for both phases were recruited from the following five tertiary care academic centers (i.e., teaching hospitals): Beth Israel Hospital, Boston, Massachusetts; MetroHealth Medical Center, Cleveland, Ohio; Duke University Medical Center, Durham, North Carolina; Marshfield Clinic/St. Joseph’s Hospital, Marshfield, Wisconsin; and the University of California, Los Angeles Medical Center, Los Angeles, California. The authors from the SUPPORT study have described the data collection procedures as virtually identical for both phases (Knaus et al, 1995).

The following general variables were collected during the first 24 hours after study entry, which was the first hospital day for all patients not in the intensive care unit (ICU). For patients in ICU, the data were collected for the first 24 hours during hospitalization after developing acute respiratory failure, coma, or multiple organ system failure (Knaus et al, 1995). These variables included the diagnostic groups, demographic variables (i.e., age, sex, race, years of education), physiologic variables such as vital signs (temperature, mean blood pressure, and heart rate), and common laboratory measures (arterial blood gases, serum creatinine, leukocyte count, serum albumin, and serum bilirubin). The diagnoses of comorbidity of type-II diabetes and dementia were also obtained at study entry. The physiologic variables and laboratory measures were collected on days 3, 7, 14 and 25 after study entry. The SUPPORT study focused on day 3 data for predicting risk for death, as all patients in the study had to survive for at least 48 hours after initial qualification for SUPPORT (Knaus et al, 1995).
All admitted patients, including those who were in the ICU, were screened daily, and all patients who met the diagnostic and severity criteria described in Appendix I were enrolled in the study (Knaus et al, 1995). Data assessment was determined by routine diagnostic and testing procedures at the five medical hospitals (Knaus et al, 1995). The follow-up period was 180 days after study entry, and survival outcome data were obtained at the end of the 180-day period. Direct 180-day follow-up was completed for 96% of patients, and the survival outcome for the other 4% were obtained from the deaths registered in the National Death Index (Knaus et al, 1995). There were no missing observations with regard to the survival outcome, the illness diagnoses, and patients’ ages.

Ongoing reliability testing of all physiologic and laboratory measures mentioned above was conducted along with the patient identification and data collection procedures (Knaus et al, 1995). A random 10% sample of patients within 3 to 10 days of the initial data collection was selected by a second nurse abstractor to test for inter-rater reliability for the general physiologic measures (i.e., temperature, mean blood pressure, and heart rate per minute). For temperature, mean blood pressure and heart rate per minute, the kappa measures were 87%, 85% and 88%, respectively. The kappa measures were 90% and 82% for Type-II diabetes and dementia, respectively (Knaus et al, 1995). In-hospital deaths during the study period were also obtained (Knaus et al, 1995).
Statistical Analysis

All analyses in this study were conducted using SAS Statistical software version 9.4 (SAS Institute Inc, North Carolina). The purpose of the statistical analyses was to determine how age modifies the effect of lung cancer on the short-term survival outcomes in severely ill, hospitalized patients. Multivariate Poisson regression with robust standard error was used for analyses. While the outcome variable was treated as binary (1=death, 0=alive), logistic regression was not used in this case, because the risk of death in the group without lung cancer (i.e., in the reference group) was around 38%, which would have violated the rare disease assumption when using odds ratios to estimate risk, which in turn would generate biased results. Cox regression analyses could not be conducted either, due to the unavailability of individuals’ time-to-event data from the original SUPPORT study dataset.

Characteristics of patients with and without lung cancer were compared by computing standardized differences of the variables between the lung cancer and reference group. P-values in this case were not computed, as the sample size for the study was relatively large, and thus even small differences would appear to be statistically different at alpha=0.05. Continuous covariates included education (years), serum bilirubin and albumin, resting heart rate (i.e. the amount of blood pumped when one is not exercising) per minute, and days of hospital stay before study entry. Categorical covariates were race, gender, and comorbidity of Type-II diabetes and dementia.

The potential effect modifier, age, was divided into tertiles as a categorical variable for easier stratification and interpretation. There were no indicated biological reasons from prior literature for categorizing age by other schema, therefore tertiles were used to maximize statistical efficiency. Patients aged equal or older than 20 and younger than 55 were in the first tertile;
those aged equal or older than 55 and younger than 68 were in the second tertile, and those aged equal or older than 68 and younger than 80 were in the third. Patients aged older than 80 and younger than 20 were excluded from analyses, as there were no one below 20 years old and no one older than 80 died of lung cancer.

Potential confounders were adjusted for in the multivariable models to minimize bias of the lung cancer-mortality association. These confounders were selected and included in the final model guided by three factors: (i) the clinical relevance of the covariates (Jemal et al, 2010), (ii) by referencing the standardized differences of these variables between lung cancer and non-lung cancer groups (standardized differences >10%) (Cohen, 1998) and (iii) by assessing the percent change of the main coefficients when adding the covariates to the model. Potential confounders that were adjusted in the final model included years of education, race, gender, comorbidity of Type-II diabetes and of dementia, and resting heart rate per minute.

In this paper, effect modification of age on lung cancer for the risk of death was evaluated first by assessing the homogeneity of effects, i.e. by stratifying on age. The risk of short-term death due to lung cancer was computed in each age tertile (Table 2.1). Differences between stratum-specific RRs would indicate presence of multiplicative effect modification. To test whether the effect modification by age was statistically significant at alpha=0.05 level, the Wald chi-square associated with the interaction term (age*lung cancer) was evaluated in the Poisson regression model.

To further evaluate the presence and direction of effect modification of age on lung cancer diagnosis, on both multiplicative and additive scales, a second analysis comparing the observed and expected joint effects of age and lung cancer was conducted. A dummy variable approach was used to create a 6 level categorical variable that represented various combinations of age
tertile groups) and lung cancer (binary) variables. The reference group consisted of the group of patients without lung cancer and were in the youngest age group (i.e., the first tertile). Table 2.0 shows the 6 levels of this categorical variable. To estimate the independent effect of lung cancer: group 2 was compared to the reference group (group 1). To estimate the independent effect of age (3rd tertile): group 5 was compared to the reference group. The observed joint effect was estimated by comparing group 6 to group 1. On the multiplicative scale, in the absence of interaction, the expected joint effect (i.e., the product of the two independent effects) would equal the observed joint effect. Therefore, the ratio of RRs (describe what this ratio of RRs is) would be 1. Similarly describe for additive interaction. (Table 2.2). Comparing the third age tertile to the first age tertile, the observed independent effect of age, the observed independent effect of lung cancer, and the observed joint effect of the two factors were obtained. The ratio of RRs for multiplicative interaction ¹ and relative excess risk of interaction ² (RERI) for additive interaction were then calculated and tested for significance.

Missing Data:

The degree and pattern of missing data were examined. There were no missing data for the outcome variable (being alive/dead), for the main exposure variable, disease diagnosis, and the effect modifier of age. For covariates adjusted in the final model, there were no missing data for

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¹ The ratio of RRs for evaluating multiplicative interaction between two binary variables, is measured by dividing the observed joint effect of two factors by the multiplication of observed individual effect: ratio of RRs=RR_{11}/RR_{10} RR_{01}. ratio of RRs<1 indicating synergistic interaction; ratio of RRs>1 indicating antagonistic interaction.

² RERI for evaluating additive interaction between two binary variables, is measured by RR_{11}-RR_{10}-RR_{01}+1. RERI=p indicating no interaction; RERI>0 indicating synergistic interaction; RERI<0 indicating antagonistic interaction.
race, gender, heart rate per minute, and comorbidity of Type-II diabetes and dementia. The missing frequency of years of education was 12% in total, 9% in the lung cancer group, and 11% in the non-lung cancer group. The frequency of missing years of education among the lung cancer and non-lung cancer groups were relatively balanced, therefore the missingness for education should not have been related to lung cancer diagnosis.

The missing data pattern was examined by looking at the distribution of fully observed variables between those with complete data for education years and those with missing education data. Chi-square tests showed that those with missing years of education data were more likely to be African American and in the oldest age group (i.e., the third tertile). There were no systematic differences on the complete observations of survival outcomes, heart rate per minute and comorbidity of Type-II diabetes and dementia between those with and without missing data of education.

Multiple imputation under fully conditional specification (FCS) was implemented, and the same Poisson regression model and covariates as the main analyses was used for analyses. Twenty complete datasets with filled-in predicted values were generated by SAS, using a linear regression model to predict missing education years, as they were continuous. Each of the 20 datasets was then analyzed using Poisson regression models (as the main analyses) to generate estimates of the missing variable. Finally, the estimates and standard errors from each analyzed dataset were pooled for further inferences.
Results:

A total of 833 (92%) patients among the lung cancer group died at the end of the 6-month follow-up period, comparing to 5368 (65%) patients among the non-lung cancer group. Compared with patients without lung cancer, those with lung cancer were more likely to be older, male, White race, more educated, and having Type-II diabetes or dementia as comorbidities (Table 1).

Overall, lung cancer was associated with around 70% increase in the risk of short-term mortality (RR=1.68; 95% CI 1.59-1.78). The effect of lung cancer diagnosis on short-term survival differed in each age group (Table 2.1). The final model was adjusted for gender, race, education years, comorbidity of diabetes and dementia, and resting heart rate per minute. According to the results, lung cancer was associated with a two-fold increase in short-term mortality in the first age tertile (RR=2.10; 95% CI, 1.78- 2.19), a 58% increase in short-term mortality in the second age tertile (RR=1.58; 95% CI, 1.47- 1.63), and a 35% increase in mortality in the third age tertile (RR=1.39, 95% CI, 1.29- 1.41). The two interaction terms between age tertile and lung cancer diagnosis were both highly significant (p<0.0001), indicating that the stratum-specific estimates were different among age groups.

Results from the second analysis comparing the observed and expected joint effect of age and lung cancer indicated the presence of effect modification of age on lung cancer on both multiplicative and additive scales, and the interaction between the two factors was antagonistic. The observed independent effect of age (3rd tertile vs. 1st tertile) on short-term risk of death was 1.45 (95% CI,1.32-1.57), and the observed independent effect of lung cancer on short-term risk of death was 2.01 (95% CI, 1.67,2.17). The observed joint effect of age and lung cancer on short-term mortality was 1.73 (95% CI, 1.66-1.83). Comparing the third age tertile to the first age
tertile, the ratio of RRs was computed to be 0.59 (95% CI, 0.49-0.62), and the RERI was -0.73 (95% CI, -0.62, -0.80). A negative RERI and a ratio of RRs less than one showed the observed joint effect of age and lung cancer is less than the expected joint effect. These results indicated that despite lung cancer was associated with a higher risk of short-term mortality, this association became less apparent as age increased.

The pooled RR estimate of education years from multiple imputation was 1.47 (95% CI: 0.97-2.40), which was similar to the RR estimate of education years obtained from the complete case analysis (RR=1.44; 95% CI: 0.89-2.36). Estimates of other variables from multiple imputation were similar to those from complete case analysis as well. For instance, under multiple imputation, the stratum-specific RRs in the fully adjusted model were 2.06, 1.54 and 1.31, which were similar in magnitude with results shown in Table 2.1.

Discussion:

Chronologic age is considered as one of many predictive factors for survival outcome in lung cancer patients because age is affected by various factors, including physiologic reserve, comorbidities, and physical performance (Lagier et al, 2014). The SUPPORT study, taking all nine disease groups as a whole, found that although increase in age resulted in decreases in physiologic reserve, therefore lowering the long-term survival rate, the incremental influence of aging on the short-term risks of death was small. In addition, according to several studies (Koppert et al, 2012), older patients are less likely to be offered standard lung cancer treatment, due to lack of concern regarding their tolerance of treatments. Though older patients could have lower tolerance for operative and non-operative treatments and higher postoperative mortality
(Lu et al, 2018), this higher risk should be weighed against the potential benefits in order to
determine their eligibility for surgery that may assist in the decision-making process as well as
the design of alternative treatment options. Recent studies have started to develop the body of
information about which chemotherapy agents are safe and effective in older adults, and also
expanded their knowledge of good palliative and supportive care (Venuta et al, 2016).

This study evaluated the interaction effect of age with the lung cancer diagnosis on short-term
survival among seriously ill, hospitalized patients. The key study findings were that though lung
cancer was inversely associated with short-term survival in general, the inverse association was
less apparent among older patients. Antagonistic effect modification of age on lung cancer was
found on both multiplicative and additive scales. These findings may shed light on policy and
decision making in physicians, patients, and patients’ families that age is used appropriately used
in treatment guidelines. For example, elderly patients and their family members should be
offered a full list of treatment options and explained about the risk and beneficial outcomes
followed by treatment. Doctors should not withhold treatment information and options to the
elderly without disclosure.

Several strengths of the study associated with the design of SUPPORT study worth noticing.
Important physiologic and demographic variables that might influence the short-term prognosis
of these patients were collected prospectively for the SUPPORT study, therefore confounding
could be minimized by adjustment. Differential misclassification of exposure, i.e., the lung
cancer disease status should be minimal, as all five participating hospitals used standardized
procedures to diagnose patients for their disease statuses. Likewise, differential misclassification
of outcome should also be minimal, as the outcome was the survival outcome of each patient,
which was objective by its nature. The inter-rater reliability of physiologic measurements had
been tested for this sample previously, and inter-rater agreement for specific comorbidities was excellent (kappa=0.9 for dementia and for type-II diabetes).

Nonetheless, there were study limitations that need to be noted. First, this study was based on a secondary analysis of a dataset collected from 1989 to 1994 when the SUPPORT study was designed and conducted, which inarguably makes it more outdated compared with other studies investigating similar subjects. The classification of diseases and disease severity and instruments for measuring physiologic and laboratory variables could have become more valid and reliable over these decades. Second, inclusion and exclusion criteria for the SUPPORT study were restricted. The original SUPPORT study only selected patients from five teaching hospitals, and study entry criteria were limited to patients diagnosed with one of nine diseases and with particular severity level. Therefore, the generalizability of study findings to other types of hospital settings and patient populations awaits further validation. Third, selection bias threatening internal validity might have existed, since the dataset did not provide information on differential loss to follow up. Because all of the data used in the study had to come from the original SUPPORT study, limiting the amount of data available for analysis, which indicates there might be residual and unmeasured confounding that could not be adjusted for in the final model. For instance, this dataset did not have information with regard to a critical confounder in the lung cancer—survival relationship, cigarette smoking. Instrumental variable analyses were not used under this circumstance, as a valid and strong instrument was difficult to be found. Also, the SUPPORT study only provided the measurements of covariates at day 3, therefore more advanced modeling of longitudinal data, such as Generalized Estimating Equation (GEE) model and mixed models, were not used to deal with missing data and account for within-subject correlations from repeated measurements. Tests for reliability and validity of measurements
other than physiologic measures also were not specified in the study. Lastly, this study, due to its longitudinal nature, should have been analyzed with Cox regression analysis, which would use time-to-event variable to account for censoring in a survival analysis. However, due to the limitation of data availability, there was no information on the time-to-event variable in the SUPPORT study.

**Conclusion**

Advanced-stage non-small cell lung cancer was associated with an elevated risk of short-term death among severely ill, hospitalized patients, yet this increase in risk was less apparent in the older age group. This study found that there was effect modification of lung cancer association with short-term mortality across strata of age on both additive and multiplicative scales, which could shed light on using chronological age appropriately to make treatment and medical decisions. Further studies with longitudinal data should be conducted to obtain more accurate survival estimates, and with a more generalizable population so references will not be confined to severely ill patients with extremely poor prognoses. These points notwithstanding, the results from this investigation suggest that aging might not proportionately increases mortality among advanced-stage lung cancer patients. Risks and benefits associated with treatment options should be weighed appropriately, and properly explained to the older patients and their families to make informed decisions.
Appendix I: Inclusion and Exclusion criteria for the SUPPORT study:

Patients were placed in the first category (the one with the lowest number) for which they qualified. They could meet the necessary criteria at time of hospitalization or at any time during treatment in an intensive care unit.

1. Nontraumatic coma

Inclusion criteria: Documentation of "coma" or "unresponsive" defined as a Glasgow coma scale score of 9 or less, lasting for 6 or more hours.

Exclusion criteria: Evidence of drug intoxication, hypothermia, or metabolic disturbances (except hypoglycemia and hypoxemia) as the primary cause of coma, general anesthesia within the previous 48 hours, determination of brain death within 48 hours of onset of coma, or patients who had a normal preoperative neurologic examination but who remain unresponsive after surgery.

2. Multiple organ system failure and malignancy

Inclusion criteria: Care in the intensive care unit, an APACHE II acute physiology score of 15 or more (12 or more if paralyzed with medications) at admission, and documentation of any solid or hematologic malignancy currently present in at least one site distant to the original location.

Exclusion Criteria: Multiple traumas, near-drowning, drug intoxication, or primary hypoventilation including that associated with the Guillain-Barre syndrome.

3. Acute respiratory failure
Inclusion criteria: Admission to the intensive care unit, documentation of suspected pneumonia or the adult respiratory distress syndrome, and an APACHE II acute physiology score of 10 (7 or more if paralyzed with medications).

Exclusion criteria: Severe chronic obstructive pulmonary disease or congestive heart failure, Pneumocystis carinii pneumonia, status asthmaticus, pulmonary embolism, immunologic lung disease, primary restrictive lung disease, primary hypoventilation including that associated with the Guillain-Barre syndrome, smoke inhalation, or a thoracotomy during current hospitalization.

4. Multiple organ system failure and sepsis

Inclusion criteria: Care in the intensive care unit, an APACHE II acute physiology score of 15 or more (12 or more if paralyzed with medications) at admission, and a clinical impression of sepsis, septicemia, or bacteremia.

Exclusion criteria: Near-drowning or drug intoxication.

5. Acute exacerbation of severe chronic obstructive pulmonary disease

Inclusion criteria: Clinical diagnosis of chronic obstructive pulmonary disease, chronic bronchitis, chronic obstructive lung disease, or emphysema with breathlessness, respiratory failure, or mental status change as the main reason for hospital admission, and hypercapnea and hypoxemia (Po2 < 60 mm Hg and Pco2 > 50 mm Hg if the patient is receiving room air, or Pco2 > 50 mm Hg alone if the patient is receiving supplemental oxygen) documented at admission.

Exclusion criteria: Status asthmaticus.
6. Acute exacerbation of severe congestive heart failure

**Inclusion criteria:** Clinical diagnosis of congestive heart failure or cardiomyopathy with an exacerbation of symptoms as the primary reason for hospital admission plus one of the following: 1) a history of severe congestive heart failure at baseline (New York Heart Association class III or IV) manifested by a history of dyspnea at rest or with minimal exertion related to primary cardiac failure, and medications before admission that include at least two drug classes (diuretics, vasodilators, or adrenocortical extract inhibitors), and a history of class III or IV congestive heart failure at hospital admission documented by dyspnea at rest at baseline; 2) a history of class IV congestive heart failure at admission, dyspnea at rest, and systolic blood pressure of 100 mm Hg or less, or a history of hypotension that precludes the use of diuretics, vasodilators, or adrenocortical extract inhibitors; and 3) documentation of severe congestive heart failure with an ejection fraction of 20% or less.

**Exclusion criteria:** Severe chronic obstructive pulmonary disease, shock, primary acute renal failure, decreased systemic vascular resistance, restrictive cardiac disease, circulatory overload, congestive heart failure resulting primarily from valvular heart disease, cardiac surgery, or thoracotomy during current hospitalization.

7. Chronic liver disease

**Inclusion criteria:** Chart documentation of cirrhosis and at least two of the following: a serum albumin level of 3.0 mg/dL or less, a serum bilirubin level of 3.0 mg/dL or more, uncontrolled ascites, hepatic encephalopathy, documentation of cachexia, or a massive gastrointestinal bleed
defined as two or more blood transfusions in 24 hours and either hematemesis or gross blood on endoscopic visualization or nasogastric tube aspiration.

8. Colon cancer with liver metastasis

**Inclusion criteria:** Known cancer of the colon or rectum and metastasis to the liver at hospital admission.

**Exclusion criteria:** New diagnosis within the previous 30 days and first hospitalization for cancer.

9. Non-small cell carcinoma of the lung

**Inclusion criteria:** Documentation of non-small cell carcinoma of the lung at hospital admission, and stage III or IV disease manifested by known involvement of the mediastinum, hilum, or peri-bronchial nodes, or known involvement of the pleural space, or known distant metastases.

**Exclusion criteria:** Cell types other than squamous cell or adenocarcinoma of the lung, new diagnosis within the previous 30 days and first hospitalization for cancer.
References:


Table I. Population Characteristics by Hospital-Diagnosed Non-Small Cell Lung Cancer Diagnosis

<table>
<thead>
<tr>
<th>Age(tertiles), N(%)</th>
<th>Lung Cancer (N=883)</th>
<th>Not Lung Cancer (N=7141)</th>
<th>Standardized Difference (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>20&lt;=age&lt;55 years</td>
<td>245 (27.8)</td>
<td>2429 (34.0)</td>
<td>20.3</td>
</tr>
<tr>
<td>55&lt;=age&lt;68 years</td>
<td>388 (44.0)</td>
<td>2287 (32.0)</td>
<td></td>
</tr>
<tr>
<td>68&lt;=age&lt;80 years</td>
<td>250 (28.3)</td>
<td>2425 (34.0)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Race, N (%)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>741 (85.3)</td>
<td>5506 (78.2)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>12 (1.38)</td>
<td>265 (16.4)</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>107 (12.3)</td>
<td>1175 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>9 (1.04)</td>
<td>96 (1.36)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender, N (%)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>554 (62.7)</td>
<td>4047 (57.5)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>329 (37.3)</td>
<td>3067 (43.0)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>aDiabetes, N(%)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>404 (45.8)</td>
<td>7000 (98.0)</td>
<td>22.4</td>
</tr>
<tr>
<td>Yes</td>
<td>479 (54.2)</td>
<td>141 (2.0)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>bDementia, N(%)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>382 (99.6)</td>
<td>6895 (96.6)</td>
<td>14.7</td>
</tr>
<tr>
<td>Yes</td>
<td>501 (0.4)</td>
<td>246 (3.4)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Education(years), Mean (SD)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>12 (3.3)</td>
<td>8 (3.5)</td>
<td>15.2</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>cHospital Stay (days), Mean (SD)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (0.3)</td>
<td>5 (9.2)</td>
<td>10.2</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>dHeart Rate/minute, Mean (SD)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>94 (27.8)</td>
<td>97 (32.0)</td>
<td>10.6</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>dAlbumin, Mean (SD)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3 (0.9)</td>
<td>2 (0.5)</td>
<td>7.6</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>dBilirubin, Mean (SD)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (2.9)</td>
<td>3 (5.3)</td>
<td>9.8</td>
<td></td>
</tr>
</tbody>
</table>

Note:

*: Comorbidity status of type-II diabetes diagnosed on day1.

*: Comorbidity status of dementia diagnosed on day1.

*: Day in hospital at which patient entered study.

*: Heart rate per minute, albumin level and bilirubin level collected on day3 of study entry.

*: Standardized difference = difference in means or proportions divided by standard error; imbalance defined as absolute value greater than 0.10 (Cohen, 1988).
Table 2.0: the 6-level categorical variables for the dummy variable approach

<table>
<thead>
<tr>
<th>Age Tertile 1 (-)</th>
<th>Lung Cancer</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (-)</td>
<td>Ref (1)</td>
<td></td>
</tr>
<tr>
<td>Yes (+)</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>No (-)</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Yes (+)</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>No (-)</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Yes (+)</td>
<td></td>
<td>6</td>
</tr>
</tbody>
</table>
Table 2.1 Stratified Analysis of Lung Cancer-Survival Relationship for each age tertile:

<table>
<thead>
<tr>
<th>Age tertile</th>
<th>Model 1 (Crude)</th>
<th>Model 2 (education years, gender, race)</th>
<th>Model 3 (education years, gender, race, heart rate, Type-II diabetes, dementia)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age tertile 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung Cancer (No)</td>
<td>1313(49)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Lung Cancer (Yes)</td>
<td>221(8)</td>
<td>1.99 (1.76,2.25)</td>
<td>2.09 (1.77,2.49)</td>
</tr>
<tr>
<td><strong>Age tertile 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung Cancer (No)</td>
<td>1551 (58)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Lung Cancer (Yes)</td>
<td>350 (13)</td>
<td>1.54(1.46,1.61)</td>
<td>1.56 (1.48, 1.65)</td>
</tr>
<tr>
<td><strong>Age tertile 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung Cancer (No)</td>
<td>1697(63)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Lung Cancer (Yes)</td>
<td>237(9)</td>
<td>1.32 (1.28,1.36)</td>
<td>1.33(1.27, 1.38)</td>
</tr>
</tbody>
</table>
Table 2.2. Analyzing Effect Modification of Age on Lung Cancer on Additive and Multiplicative Scale

<table>
<thead>
<tr>
<th>Age</th>
<th>Lung Cancer</th>
<th></th>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No</td>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RR</td>
<td>95%CI</td>
<td></td>
<td>RR</td>
<td>95%CI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20&lt;=age&lt;55</td>
<td>ref</td>
<td>--</td>
<td></td>
<td>2.01</td>
<td>1.77</td>
<td>2.17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55&lt;=age&lt;68</td>
<td>1.23</td>
<td>1.18-1.30</td>
<td></td>
<td>1.89</td>
<td>1.75-1.99</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>68&lt;=age&lt;80</td>
<td>1.45</td>
<td>1.32-1.57</td>
<td></td>
<td>1.73</td>
<td>1.66-1.82</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additive interaction</td>
<td>RERI= -0.73, (95% CI, -0.62, -0.80)</td>
<td></td>
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<tr>
<td>Multiplicative interaction</td>
<td>Ratio of RRs= 0.59, (95% CI, 0.49, 0.62)</td>
<td></td>
<td></td>
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</tbody>
</table>

*Adjusted for education years, gender, race, heart rate per minute, and comorbidity of Type-II diabetes

Ψ RERI = 1.55 - (1.54 + 1.17) + 1 = -0.16 < 0 (95% C.I. -2.36, -0.03), indicating antagonistic interaction in the additive scale