Research Article

Social Determinants of Non-Small Cell Lung Cancer Stage at Diagnosis and Survival in Nebraska

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Abstract

Background: Lung cancer is one of the leading cancers in both incidence and mortality in Nebraska. We investigated how social determinants were associated with the stage at diagnosis and survival time for Nebraska non-small cell lung cancer patients.

Methods: A total of 12,821 NSCLC cases diagnosed between 1995 and the end of 2012 were identified using the Nebraska Cancer Registry database linked with the census tract poverty level. General logistic regression model was used to analyze the relationship between social factors and stage at diagnosis, and Cox proportional hazard model was used to investigate the adjusted effect of social factors on lung cancer survival.

Results: Among 12,821 lung cancer patients, 2,954 (23.04%) were diagnosed in situ or at localized stages and 9,867 (76.96%) were diagnosed at more advanced stages. Male gender, younger age, Hispanic origin, rural residency and being single were associated with increased ORs of being diagnosed at advanced stages. In survival analysis, patients being single at the time of diagnosis were related with 1.23 time's greater hazard of death, compared to patients who were married. The adjusted hazard ratio was also associated with the type of insurance used (p < 0.0001).

Conclusions: Both stage at diagnosis and survival time for NSCLC were associated with different social determinants. Health care providers should provide more emphasis on educating minority populations, patients living alone, and patients with limited insurance coverage about early diagnosis and follow-up care of lung cancer.

ABBREVIATIONS

NSCLC: Non-Small Cell Lung Cancer; NCR: Nebraska Cancer Registry

INTRODUCTION

Lung cancer is the second most common cancer in both men and women in the United States, following prostate cancer in men and breast cancer in women. It accounts for about 27% of all cancer-related deaths and is by far the most fatal cancer for both genders [1]. Non-small cell lung cancer (NSCLC), the most common type of lung cancer, accounts for about 85%-90% of lung cancer cases. Recent trend shows the stage at diagnosis for NSCLC has shifted towards late stages, with stage IV patients consisting 38.4% of the newly diagnosed cases [2]. The survival rates for patients diagnosed with NSCLC highly depend on the stage at diagnosis, with 5-year survival rate of about 45% among patients diagnosed with localized stages, decreasing sharply to below 20% among patients diagnosed with distant stages [1]. The strategy of treatment and care, the prognosis, and the quality of life also highly depend on the stage at diagnosis, whereas the disparity in NSCLC early detection and staging is known to be associated with certain social factors [3-5]. This study aims to identify potential social factors that predict the stage at diagnosis

and survival for lung cancer patients in Nebraska. Positive findings in this study may serve as implications for lung cancer education and strategy making on early detection for lung cancer patients and their practitioners or clinicians in Nebraska.

MATERIALS AND METHODS

The data used in this study is retrieved from the Nebraska Cancer Registry (NCR) database, and the time frame was restricted to the years 1995 to 2012; this time frame was selected so that the 2000 Census and 2010 Census poverty level data could be linked to and utilized with the NCR data. We excluded patients with ICD-O-3 SEER site/histology code indicating small cell carcinoma (8041, 8042, 8043, 8044, and 8045) and identified 14,758 patients whose primary diagnosis was non-small cell lung cancer. These patients were diagnosed in the state of Nebraska at the time of diagnosis. The Census 2000 or 2010 data was used to identify the neighborhood where the patients lived. The stage of cancer at diagnosis was obtained from the SEER Summary Stage. Patients diagnosed before January 1, 2001, were assigned a summary stage according to *Summary Stage Guide, Cancer Surveillance Epidemiology and End Results Reporting, SEER Program,* April 1977 [6]. For those who were diagnosed before January1, 2001, we assigned the summary stage according to *SEER Summary Staging Manual, 2000* [7] to them. For patients diagnosed after December 31, 2003, we assigned them the derived "SEER Summary Stage 2000" from the CS algorithm (or EOD codes), which was effective with 2004 diagnoses. We coded the summary stage as two categories: In situ/Localized and Regional/Distant, and those who were either with unknown stage or un-staged were excluded from the analysis, resulting in 12,821 patients being included in the anal.

Social Determinants

Social factors of interest were obtained from the NCR database linked with the census tract data. In our study, we analyzed the following patient's social factors: race, ethnicity, marital status, residential status, insurance status, and neighborhood poverty level. All of these social factors were obtained at the individual level by the NCR data, except that the poverty level was obtained at census tract level from the 2000 and 2010 U.S. Census data. Race was classified into "White", "Black" and "Other races" and ethnicity was classified into "Hispanic origin" or "Non-Hispanic origin" based on the self-identity of ethnicity. Marital status was categorized into being single at the time of diagnosis due to any reason (never married/separated/divorced/widowed) and being married at diagnosis. Insurance type was classified into five categories (no insurance, private insurance, Medicare, Medicaid, other), depending on which specific insurance was the patients' primary payment method. The residential status was classified into rural residence and urban residence according to the Rural –Urban Continuum 1993 [8] and 2000 as provided by the Office of Management and Budget (OMB). The poverty level obtained from the Census Tracts data was grouped into three categories: neighborhood with the percentage of population living in poverty less than or equal to 10%, between 10% and 20%, or more than 20% indicating living in a poor neighborhood.

Statistical Analysis

All statistical analyses were conducted using SAS 9.3 (SAS

Institute Inc., Cary, NC, USA). Descriptive statistics for all independent variables versus the stage at diagnosis were used to describe the characteristics for lung cancer patients. General logistic regression model was used as the main method to analyze the simultaneous influence of social determinants on the stage of diagnosis for lung cancer. We examined two-way interactions between social factors using the Wald test statistics. We also investigated interactions between poverty level and residential status, marital status, and insurance status, respectively.

For the analysis of survival time, the Cox proportional hazard model was used and the effects of stage of diagnosis and patients' age were controlled to investigate other social factors. Each variable was tested for the assumption of proportional hazard after the initial model by checking the stratified -Log-log plots.

RESULTS AND DISCUSSION

Results

Descriptive statistics of the 12,821 patients were obtained and shown in (Table 1).

Among the 12,821 patient diagnosed with lung cancer from 1995 – 2012 residing in the state of Nebraska, about 23.04% of them (n = 2,954) were diagnosed in situ or at localized stages, and the rest were diagnosed at regional or distant stages (n = 9,867). The average age of patients diagnosed with early stage lung cancer was 70.35 years, and 69 years for those diagnosed with later stages. The t-test with unequal variances showed the average ages at diagnosis for early stage and advanced stage lung cancer were significantly different ($p < 0.0001$).

For each categorical variable, the chi-square test was performed to explore potential significant effect across levels. Male patients outnumbered female patients in overall lung cancer incidence in Nebraska, and they were more likely to be diagnosed in late stages compared to female patients with a significant unadjusted effect ($p < 0.0001$). Being Hispanic was also related to a higher chance to be diagnosed at late stage ($p = 0.0076$) compared to being non-Hispanic. Patients' insurance type ($p < 0.0001$) was significantly associated with lung cancer stage at diagnosis as well. No significant co-linearity was found between these variables.

Social determinants of stage at diagnosis: The general logistic regression model was used to investigate the influence of social factors simultaneously. At the first step, we included all the variables of interest in our initial model, and we used backward selection to eliminate the factors that were not statistically significant related to cancer stage at diagnosis. The adjusted effects of patients' race ($p = 0.7959$), insurance type ($p = 0.0812$) and neighborhood poverty status ($p = 0.5760$) were not significant so were excluded from the model. After the backward selection, the model was rerun with the remaining variables to obtain the adjusted estimated odds ratio to be diagnosed at advanced stage. The result in (Table 2) indicated that patients' age ($p < 0.0001$), sex ($p < 0.0001$), ethnicity ($p < 0.015$), rural residency ($p < 0.0132$) and marital status ($p < 0.0379$) were related to non-small cell lung cancer stage and could be used to predict the stage at diagnosis. Elder patients were slightly more likely to be diagnosed at earlier stages, with an adjusted

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Table 1: Patient characteristics by lung cancer stage at diagnosis.

Characteristics	Stage at Diagnosis						p-value for t-test/ Chi-Square test
	In situ / Localized (n = 2,954)		Regional / Distant (n = 9,867)		Total (n = 12,821)		
	Mean	SD	Mean	SD	Mean	SD	
*Age at Diagnosis	70.35	10.36	69.00	11.08	69.31	10.93	< .0001
	n	Column %	n	Column %	n	Column %	
*Sex							< .0001
Male	1,586	53.69	5,842	59.21	7,428	57.94	
Female	1,368	46.31	4,025	40.79	5,393	42.06	
Race							0.4602
White	2,835	95.97	9,417	95.44	12,252	95.56	
Black	93	3.15	348	3.53	441	3.44	
Other	26	0.88	102	1.03	128	1.00	
*Ethnicity							0.0076
Non-Hispanic origin	2,914	98.65	9,657	97.87	12,571	98.05	
Hispanic origin	40	1.35	210	2.13	250	1.95	
Marital Status							0.3211
Single	1,157	39.17	3,859	39.11	5,016	39.12	
Married	1,722	58.30	5,707	57.82	7,427	57.93	
Unknown	75	2.54	303	3.07	378	2.95	
Residential Status							0.0585
Urban	1,484	50.24	4,711	47.75	6,195	48.32	
Rural	1,175	39.78	4,112	41.67	5,287	41.24	
Unknown	295	9.99	1,044	10.58	1,339	10.44	
*Insurance Type							<.0001
No insurance	74	2.51	271	2.75	345	2.69	
Private insurance	362	12.25	1,216	12.32	1,578	12.31	
Medicaid	48	1.62	242	2.45	290	2.26	
Medicare	1,691	57.24	5,136	52.05	6,827	53.25	
Other	779	26.37	3,002	30.42	3781	29.49	
Neighborhood Poverty Level							0.4738
<= 10%	1,382	46.78	4,735	47.99	6,117	47.71	
10% - 20%	1,362	46.11	4,467	45.27	5,829	45.46	
> 20%	210	7.11	665	6.74	875	6.82	

* Indicates an unadjusted statistically significant effect (p < 0.05) exists within the variable.

odds ratio (OR) of 0.988 (95% CI, 0.984 – 0.992) for a diagnosis of advanced stage per 1-year increment in age. Female patients were less likely to be diagnosed at later stages compared to male patients. The adjusted odds for female patients being diagnosed at later stages were 0.787 times (95% CI: 0.722 – 0.857) the odds for male patients. In terms of ethnicity, patients of Hispanic origin had an adjusted odds ratio that was 1.529 times (95%CI: 1.086 – 2.152) that of patients of non-Hispanic origin, indicating that Hispanic patients were more likely to be diagnosed at later stages after adjusting for other demographic and socioeconomic factors. Patients living in rural areas of Nebraska had an adjusted odds ratio of 1.118 (95% CI: 1.024 – 1.221) to be diagnosed at later

stages compared to patients living in urban areas; and patients being married at diagnosis were less likely to be diagnosed at later stages compared to patients who were never married, separate, divorced or widowed with an adjusted OR of 0.910 (95% CI: 0.833 - 0.995). No significant co-linearity or interactions were found between these variables.

Social determinants of lung cancer survival: By the end of year 2012, only 1,768 patients still survived out of the 12,821 patients. Among the rest 11,053 patients who died during this time period, six thousand nine hundred and seventy-four (6,974) patients died from non-small cell lung cancer based on the ICD-10 diagnosis code recorded by the cancer registry. We

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categorized the patients dying from NSCLC as events, and the remaining as censored data in the survival analysis to investigate how social determinants were associated with lung-cancer-specific survival. Patients dying from NSCLC were diagnosed with lung cancer at 69.67 years on average, which was slightly later than the overall average age at diagnosis for NSCLC patients (69.31 years). The mean and median survival time between cancer diagnosis and death was 14.36 months and 7.30 months respectively for patients who died from NSCLC. On the other hand, patients who still lived by the end of 2012 or died from other reasons had the mean and median survival time of 26.22 months and 10.53 months respectively. Further investigating the survival time between diagnosis and death within lung cancer patients, we found the median survival time for early stage lung cancer patients (20.6 months) were approximately 3.3 fold than the mean survival time for late stage patients (6.2 months). The survival time for patients dying from NSCLC or not, and the survival time breakdown by stage for patients dying from NSCLC is shown in (Table 3). The survival probability over time suggests a significant difference for patients diagnosed with early and late stage lung cancer and therefore the stage at diagnosis should be controlled in survival analysis.

We used the Cox Proportional Hazards model adjusting for stage at diagnosis and age at diagnosis to conduct the analysis. The result of the Cox proportional hazards model indicated that patients' gender, insurance type, marital status and residency were social determinants that were related to the survival probability over time after adjusting for stage at diagnosis and age. Patients diagnosed with late stage had a 3.845 times higher adjusted hazard of death compared to patients diagnosed with early stage (95% CI: 3.588 – 4.121, p < 0.0001). Female patients tended to have lower hazard of death than male patients. On average, female patients experienced 0.839 times (95% CI: 0.798 – 0.881, p < 0.0001) the risk of death compared to male patients of the same age and stage controlling for other social determinants. Results also showed that patients who were married and living with their spouses had significant lower risk of death. That is, being single due to any reason (never married/separate/

Table 2: The adjusted estimated odds ratios for being diagnosed at advanced stages.

Effect	P-value	Estimated OR	95% Wald Confidence Limits	
Age	<.0001	0.988	0.984	0.992
Female vs. Male	<.0001	0.787	0.722	0.857
Hispanic origin vs. Non-Hispanic origin	0.0150	1.529	1.086	2.152
Rural vs. Urban residency	0.0132	1.118	1.024	1.221
Married vs. Single	0.0379	0.910	0.833	0.995

Table 3: Survival time for patients dying from NSCLC compared with patients alive/dying for other reasons.

Survival Time	n	Mean ± SD	Median
Patients dying from NSCLC	6,974	14.36 ± 20.00	7.30
In situ / Localized	971	30.25 ± 30.20	20.60
Regional / Distant	6,003	11.79 ± 16.43	6.20
Patients alive/dying for other reasons	5,847	26.22 ± 35.22	10.53

**Table 4:** The adjusted hazard ratios of risk factors that are related to NSCLC survival.

Risk Factors	P-value	Adjusted Hazard Ratio	95% Hazard Ratio Confidence Limits	
Age	<.0001	1.009	1.006	1.011
Advanced stage vs. Early stage	<.0001	3.845	3.588	4.121
Female vs. Male	<.0001	0.839	0.798	0.881
No insurance vs. Private insurance	0.8756	1.012	0.871	1.176
Medicaid vs. Private insurance	0.0004	1.322	1.134	1.542
Medicare vs. Private insurance	<.0001	1.249	1.152	1.355
Other insurance vs. Private insurance	<.0001	0.648	0.594	0.707
Rural vs. Urban residency	0.0100	1.068	1.016	1.122
Married vs. Single	<.0001	0.814	0.773	0.856

divorced/widowed), increased the hazard of death by about 1.23 times (95% CI: 1.164 - 1.294, p < 0.0001) after adjusting for other factors. Rural residency was also related to a slight increase in the hazard ratio of death compared to urban residency (HR = 1.068, 95% CI: 1.016 – 1.112, p = 0.01). The insurance type of patients' primary payment method was also found to be independently associated with NSCLC survival. Although there was no significant decrease in hazard ratio of death with patients covered by private insurance compared to patients without insurance (p = 0.8756), those with private insurance outperformed patients with Medicare and Medicaid in survival time after adjusting for other social determinants. On average, patients with Medicaid as their primary payment method had a 1.322 times adjusted hazard of death (95% CI: 1.134 – 1.542, p = 0.0004), and patients with Medicare as primary payment method had a 1.249 times adjusted hazard (95% CI: 1.152 – 1.355, p < 0.0001) compared to patients covered with private insurance.

Results from the Cox Proportional Hazards model indicated that other factors such as neighborhood poverty level (p = 0.3789), race (p = 0.5370) and ethnicity (p = 0.1167) were not significantly associated with the survival probability for non-small cell lung cancer patients in Nebraska. The Kaplan-Meier curves for all significant variables were illustrated in (Figure 1).

Discussion

The Nebraska Cancer Registry (NCR) was founded in 1986 and began collecting data in 1987, and is managed by the Nebraska Department of Health and Human Services. For 16 consecutive years (1995-2010), the NCR has met all of the criteria necessary to earn the Gold Standard of data quality awarded by the North American Association of Central Cancer Registries (NAACCR). This study was able to connect the Nebraska Cancer Registry database and census tract poverty data to investigate the relationships between major social determinants and stage at non-small cell lung cancer diagnosis and survival for Nebraska patients who were diagnosed between the years 1995 and 2012. The linkage between the two databases allowed us to conduct more comprehensive analyses on NSCLC patients in Nebraska,
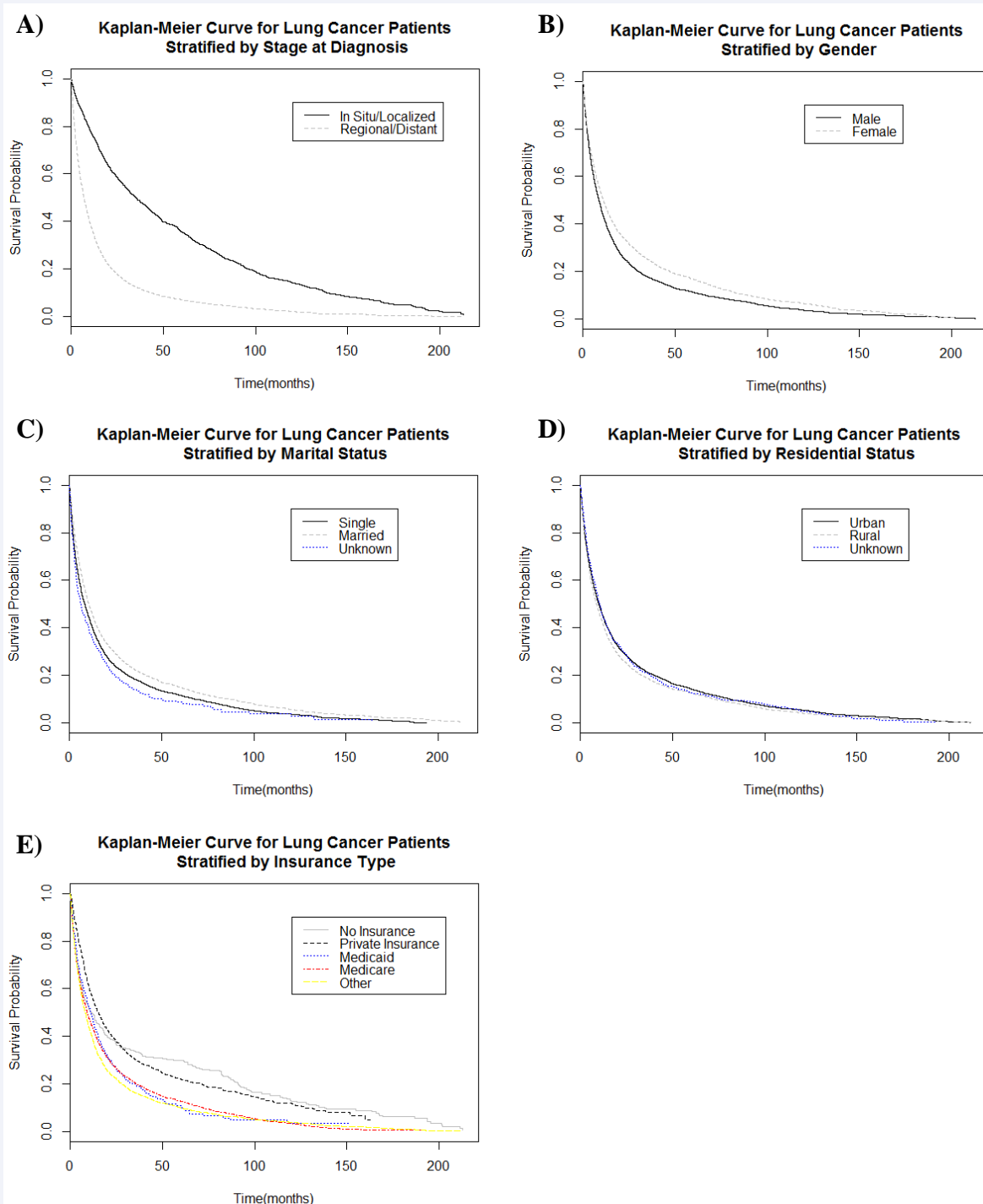
Figure 1 Kaplan-Meier curves for significant factors related to lung cancer survival.

and it also made this study unique that major socioeconomic indicators included in the NCR data and in the census tract poverty level data were utilized simultaneously so that the effect of a specific indicator could be well controlled for other indicators in the analyses.

The key findings of this study include identifying statistically significant relationships between indicators of

social determinants and both stage at diagnosis and mortality risk for non-small cell lung cancer. Our finding indicates with increased age, there is a slight decrease in odds of late stage diagnosis; this result confirms the findings from previous studies [9,10], and extends the evidence by controlling for other social determinants, that lung cancer is indeed initially seen at earlier stage with increasing age, which may be explained that elder people undergo more medical services due to other co

morbidities and more frequently have lung cancer detected at an early asymptomatic stage. Gender was associated with both the stage at diagnosis and the adjusted survival probability for NSCLC patients. Female patients were less likely to be diagnosed at late stage and had lower hazard of death after controlling for other factors. This result corresponds to publish reports that explained this discrepancy because males were more likely to be exposed to cigarette smoking, which contributes to higher lung cancer incidence in males [11,12].

Hispanic origin is another independent risk factor for being diagnosed at late stages. The effect of ethnicity on late diagnosis is the strongest among all predictors that we investigated in this study, and the odds that patients of Hispanic origin being diagnosed with late stages are on average 1.53 times that of non-Hispanic patients. Haiman et al. observed ethnic and racial differences in lung cancer risk associated with smoking among both men and women and for all histologic types of lung cancer [13]. The disparity rising from patients' ethnicity also highlights the importance of addressing social and cultural factors, which might limit the access to early detection for lung cancer in several ways, both internal and external, including low interest in screening or early detecting, denial of risks or fear, the availability of information in languages, distance or ease of transportation to medical facilities and so on [14]. As most Hispanic populations are concentrated in certain communities such as those in South Omaha, Nebraska, the evidence in such disparity can serve as an implication that such areas and communities may need more emphasis on the education as well as the early detection of lung cancer.

Our study also suggests that patients living in rural areas are more likely to be diagnosed at late stages compared to patients living in urban areas. A previous review shows that rural residents may have lower cancer incidence and mortality, but conversely, the proportion of rural patients diagnosed at advanced stages is higher, suggesting that rural patients are disadvantaged in obtaining certain medical services compared to their urban counterparts [15]. In terms of early detection of diseases, or say, preventive healthcare services, it is challenging for such services to actively reach certain rural areas, and as a result, rural residents are significantly less likely than urban residents to obtain certain preventive health services, such as mammogram as a routine screening for breast cancer, after controlling for demographic characteristics and health insurance status [16].

Undoubtedly, the stage at diagnosis for NSCLC is a dominant factor that influences the survival of the patients. The adjusted hazard ratio suggests that patients with advanced stages at diagnosis have a 3.85 folds risk of death compared to patients with early stages. But it is not the sole factor that can affect the survival probability for NSCLC patients. Further investigation on lung cancer survival, after controlling for the stage at diagnosis and patients' age, suggests that the survival probability over time depends not only on the clinical features of NSCLC patients but also on certain social determinants, which can predict the mortality risk independently. In our study, being married and living with spouses is related with 18% less mortality risk compared to never married, widowed, separated or divorced patients. This finding suggests that social connection among family members play a

positive role in cancer survival, which can be explained by the feature of social networks in cancer prevention and survival. This result corresponds to a previous study based on medical records review conducted by Greenberg and colleagues, who concluded that the presence of a spouse accounted for at least in part for the choice of treatment; often more aggressive choices were made for a patient with lung cancer, which resulted in a lower mortality risk compared to single patients [17]. Plus, a previous study shows that marital status may influence the treatment strategy for lung cancer, and more aggressive treatment is more likely to be assigned to patients who are married [18], and even controlling for stage and treatment, married patients turn out to have better survival [17].

Because of the linkage between the Nebraska Cancer Registry data and the census tract neighborhood poverty level data, it was possible to look at two socioeconomic determinants indicating patients' financial resources and access to medical services: insurance type and neighborhood poverty level simultaneously. Our study suggested that the determination of both lung cancer stage at diagnosis and survival was not related to patients' poverty level, whereas, the survival of NSCLC patients was significantly associated with the insurance type. Thus we conclude when encountering these two socioeconomic variables, the insurance type may outperform patients' poverty level and therefore be a better indicator reflecting patients' financial status to predict cancer survival. Particularly, governmental insurance programs (Medicare and Medicaid) performed more poorly in prolonging survival among NSCLC patients compared to private insurance. The result shows there is no significant difference in the survival probability over time between private insurance holder and patients without any insurance, while the survival probability for patients with private insurance outperformed that for patients covered by Medicare and Medicaid. There is little evidence from which we can infer why patients with no insurance did not perform worse in survival compared to patients with private insurance; we speculate it may be due to the fact some communities in Nebraska such as Lincoln and Omaha have groups that work with physicians to provide free care to uninsured patients, and hospitals and cancer centers provide "charity care" to uninsured population as well. As we conjecture, there may be fewer stigmas attached to free/charity care than to Medicaid, yet it needs further evidence to prove. Apart from this, a review of the impact of health insurance coverage on health in 2002, indicated that many studies of overall health status, cancer outcomes, and hospital-based care have found that adults with Medicaid coverage frequently fare no better than uninsured patients in their health-related outcomes, and the reason may be because that patients may become eligible for Medicaid as a result of poor health, and the programmatic features of Medicaid, including provider participation and payment levels and limited coverage periods, contribute to worse health-related outcomes [19]. For patients with Medicare as their primary payment method, Rowland and Lyons argue that although Medicare coverage offers basic health insurance to promote access to care, yet for those who have the most health needs, in this case patients who need care for cancer, financial concerns can impede access to needed medical care [20]. Researchers also claim that Medicare beneficiaries in poor health are more likely to report barriers to medical care than beneficiaries with better health

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[21]. In addition, the disparity in lung cancer survival can also be attributable to the quality of treatment and care received through different insurances, and for patients with the same other characteristics, more aggrieve treatments are more likely to be given to those with private insurance compared to those with Medicare or Medicaid as their primary payment method [17].

Limitations of this study include failure to take some other important social determinants into consideration due to the incomplete information that could be drawn from the database. Smoking status, for example, is a confounding factor that is related with lung cancer incidence and survival, and is likely correlated with gender [11,12]. Besides, although we did not find co-linearity between any pair of the social determinants, some researchers believe that different choice of socioeconomic indicators may lead to disparate conclusions, and potential confounding factors should be considered; therefore, the selection of the underlying social determinants, especially those indicating income equality, should be scrupulously conducted [22]. The study can also be refined by more detailed classification for lung cancer stage. Although SEER Summary Staging used in this study is considered as a good way to summarize the stage at diagnosis for cancer patients, the TNM clinical staging is also widely used in recent years and can be more accurate and comprehensive. Analysis with more detailed staging information could lead to more solid conclusions and may potentially observe the relationship between staging and social determinants with a linear trend.

CONCLUSION

This study provides a comprehensive analysis on the effects of social determinants placed on the stage at diagnosis and survival for Nebraska non-small cell lung cancer patients based on the Nebraska Cancer Registry and Census Tract poverty level data from 1995 to 2012. Hispanic patients are more likely to be diagnosed at advanced stages. Male, rural, and patients with no spouse are associated with both late stage diagnosis and higher risk of death, and patients with certain types of health insurance also have significant higher mortality risk after controlling for other factors. Patient-Centered lung cancer education, screening and early diagnosis should be emphasized and these programs should be extended to high-risk ethnical communities and rural areas to improve the lung cancer prognosis, and available medical services should be improved for patients carrying governmental health insurances to promote lung cancer survival.

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