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Research Article

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Comorbidity and Survival in Lung Cancer Patients

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Abstract

Background: As the population of the United States ages, there will be increasing numbers of lung cancer patients with comorbidities at diagnosis. Comorbid conditions are important factors in both the choice of the lung cancer treatment and outcomes. However, the impact of individual comorbid conditions on patient survival remains unclear.

Methods: A population-based cohort study of 5,683 first-time diagnosed lung cancer patients was captured using the Nebraska Cancer Registry (NCR) linked with the Nebraska Hospital Discharge Data (NHDD) between 2005 and 2009. A Cox proportional hazards model was used to analyze the effect of comorbidities on the overall survival of patients stratified by stage and adjusting for age, race, sex, and histologic type.

Results: Of these patients, 36.8% of them survived their first year after lung cancer diagnosis, with a median survival of 9.3 months for all stages combined. In this cohort, 26.7% of the patients did not have any comorbidity at diagnosis. The most common comorbid conditions were chronic pulmonary disease (52.5%), diabetes (15.7%), and congestive heart failure (12.9%). The adjusted overall survival of lung cancer patients was negatively associated with the existence of different comorbid conditions such as congestive heart failure, diabetes with complications, moderate or severe liver disease, dementia, renal disease, and cerebrovascular disease, depending on the stage.

Conclusions: The presence of comorbid conditions was associated with worse survival. Different comorbid conditions were associated with worse outcomes at different stages.

Impact: Future models for predicting lung cancer survival should take individual comorbid conditions into consideration.
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Introduction

Despite the decline in lung cancer incidence rates over the past decade, lung cancer remains the leading cause of cancer deaths among both males and females in United States. Lung cancer accounts for an estimated 27% of total cancer deaths and 13% of new cancer cases in United States (1). Advances in medical science have contributed to the increase of 1-year survival rates for lung cancer patients; however, the overall 5-year survival remains low (1). Age, gender, lung function, stage, performance status, and comorbidity are among factors affecting the survival of lung cancer patients (2).

Incidence of lung cancer is higher among older patients, and the prevalence of comorbidity is higher in these patients compared with younger patients (3). The effect of comorbid conditions on survival has drawn high research interest, although the results are inconsistent. Some studies showed comorbidity as being an independent prognostic factor for lung cancer survival (4–6). The Charlson Comorbidity index is the most widely utilized tool for evaluating the comorbidity burden in patients with chronic disease (7). However, this score does not seem to consistently predict for outcomes in lung cancer patients with some (6) but not all studies (8, 9) demonstrating worse outcomes with increasing comorbidities.

Comorbidity potentially affects lung cancer survival in several ways. Certain conditions, including chronic obstructive lung disease, cerebrovascular diseases, heart failure, and myocardial infarction were found to have an independent negative effect on survival. In addition, comorbid conditions could camouflage the cancer symptoms and cause delay in the diagnosis, although another possibility was that some lung cancer patients could be diagnosed at an earlier stage through regular observation of other chronic disease (3). In any case, the presence of comorbidities could prevent complete diagnostic evaluation leading to less accurate staging. Comorbidity also influences treatment selection, preventing patients from receiving aggressive lung cancer treatment (3, 4, 10). Furthermore, comorbidity could associate with the morphology, histology, differentiation, proliferation status, as well as with growth rate of the cancer itself, thus affecting the prognosis. Comorbidity may also increase the risk of complications and 30-day postoperative mortality after surgery (11), and the risk for complications increases as the comorbidity index score increases (12).

Most of the studies aggregated comorbidity into a comorbidity index (most frequently the Charlson comorbidity index) with little consideration of how specific conditions affected outcomes individually. The aim of the current study was to not only examine the overall comorbidities, but also individual comorbidities in their contribution to survival of lung cancer patients when controlling for other factors.

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Materials and Methods

Data on a total of 6,551 lung cancer patients statewide were captured using the Nebraska Cancer Registry (NCR) linked with the Nebraska Hospital Discharge Data (NHDD) between 2005 and 2009, and followed up to December 31, 2010 or until death/censored, given 1 year lag period afterwards. NCR is population based and is initially collected information on only newly diagnosed primary cancers by the system (13). The NHDD to be linked with cancer registry data were provided by Nebraska Hospital Association. There were inpatient and outpatient including emergency visit (ER) information initially collected by 87 acute care hospitals from 2005 to 2009 within the state (13). A detailed description of the NCR, NHDD data, and the linkage methodology has been described previously and demonstrate a linkage rate of 97% for lung cancer patients (13). For each patient in the NCR, the linkage provides important comorbidity information that was not available in regular cancer registry database. The 2005 and 2006 NHDD only had 10 diagnosis codes originally, while 25 diagnosis codes were included in the other years. The sensitivity of identifying the comorbidities of our interest using diagnosis codes included in 2005–2006 was over 99% in years where 25 diagnosis codes were provided. We excluded trans-sexual patients and those have missing values for stage or were recorded as "un-staged." If a patient had two or more records in the cancer registry database, only the first lung cancer diagnosis record was retained. Patients whose hospital discharge records were missing were also excluded from this analysis. The overall sample size after exclusion was 5,683 patients.

The data were considered secondary in that each patient record could only be identified at the state level. The patient's age at diagnosis was categorized into five age groups (0–44, 45–54, 55–64, 65–74, and 75+), and lung cancer stages were summarized as localized, regional and distant lung cancer based on SEER summary staging (14). For descriptive statistics, the proportions for all categorical variables were compared by the Pearson χ^2 test and the Mantel–Haenszel χ^2 test. Log-rank tests were used to compare survival times between patients with and without comorbidities.

Cox proportional hazards models were used to assess the effect of comorbidities on the overall survival of lung cancer patients in two ways: (i) the overall survival for lung cancer patients with comorbidities compared with those without comorbidities and (ii) the overall survival for lung cancer patients with any one of the 14 particular comorbidities compared with those without such particular comorbidity. The 14 comorbidities were myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, mild liver disease, diabetes without complications, diabetes with complications, paraplegia and hemiplegia, renal disease and moderate, or severe liver disease. These conditions were chosen based on the adaptation of the Charlson Comorbidity Index used in other studies using administrative databases (15). Two of the comorbidities (malignancy and metastatic carcinoma) could have been the result of the lung cancer itself, and AIDS patients were not captured using this database; hence these three conditions were excluded.

In multivariate analyses, the models were adjusted for age, race, sex, and histology, as well as stratified by cancer stage. Survival was calculated from the date of diagnosis to the last date of contact according to the NCR records. Patients were considered as censored if no death was recorded at their last date of contact. HR, *P* values, and 95% confidence intervals (CI) were given for the model and all statistical analyses were performed by SAS version 9.4.

Results

Of the 5,683 lung cancer patients who met the criteria for inclusion in this analysis, 3,741 (65.8%) died by the end of the data collection period. In this cohort, 1,517 (26.7%) patients did not have comorbidities of our interest at diagnosis. The majority of patients, 3,036 (53.4%) had distant (metastatic) lung cancer. Adenocarcinoma was the most commonly seen histologic subtype (34.1%). For those patients who had comorbidities, the most common comorbidities were chronic pulmonary disease (52.5%), diabetes (15.7%), and congestive heart failure (12.9%). The demographic data are shown in Table 1.

Male gender, small cell, large cell, and other cell carcinomas (comparing with adenocarcinoma) were associated with lung cancer diagnosed at a more advanced stage, while patients with squamous cell carcinoma tend to be diagnosed at a less-advanced stage compared with adenocarcinoma ($P < 0.0001$). However, patients with comorbid conditions were more likely to be diagnosed at an earlier stage ($P < 0.0001$) after controlling for age, race, gender, and histologic type (Table 2).

On survival analysis, Kaplan–Meier curves showed that patients with comorbidity appear to have poorer survival within each stage and the difference of survival between patients with and without comorbidity seem to be greater in less-advanced stages (Fig. 1). After adjusting for age, race, gender, and histologic type, the presence of comorbidity was associated with worse overall survival for lung cancer patients (Table 3). And it seemed that the impact of comorbidity was relatively greater in less-advanced cancer patients, which was shown in the decreasing point estimates of the HRs of localized (HR, 1.316), regional (HR, 1.228), and distant (HR, 1.075) lung cancer.

When stratified by stage, the overall survival was negatively associated with the presence of different comorbidities after controlling for age, gender, race, and histologic subtype (Table 3). The survival of localized lung cancer patients was negatively associated with congestive heart failure (HR, 1.731; 95% CI, 1.33–2.253), diabetes with complications (HR, 2.167; 95% CI, 1.122–4.185), and moderate or severe liver disease (HR, 3.736; 95% CI, 1.088–12.826). In contrast, the survival of patients with regional disease was negatively associated with congestive heart failure (HR, 1.258; 95% CI, 1.041–1.521), dementia (HR, 2.332; 95% CI, 1.202–4.524), and renal disease (HR, 1.437; 95% CI, 1.099–1.879), whereas the survival of patients with distant disease was negatively associated with congestive heart failure (HR, 1.186; 95% CI, 1.05–1.399) and cerebrovascular disease (HR, 1.265; 95% CI, 1.079–1.484).

Discussion

In the present analysis, 36.8% of the patients survived their first year after lung cancer diagnosis with a median survival is 9.3 months for all stages combined. The overall 1-year survival was 72.3%, 50.0%, and 21.2% for localized, regional, and distant lung

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Table 1. Descriptive statistics by stage

	Stage				
	Localized (*N* = 1,132)	**Regional (*N* = 1,515)**	**Distant (*N* = 3,036)**	**All (*N* = 5,683)**	***P*[a]**
Male	556 (49.1%)	834 (55%)	1,703 (56%)	3,093 (54.4%)	0.0002
Comorbid conditions present	891 (78.7%)	1,165 (76.8%)	2,110 (69.4%)	4,166 (73.3%)	<0.0001
Age					
0–44	18 (1.5%)	24 (1.5%)	54 (1.7%)	96 (1.6%)	<0.0001
45–54	66 (5.8%)	125 (8.2%)	292 (9.6%)	483 (8.4%)	
55–64	209 (18.4%)	319 (21%)	687 (22.6%)	1,215 (21.3%)	
65–74	421 (37.1%)	523 (34.5%)	968 (31.8%)	1,912 (33.6%)	
75+	418 (36.9%)	524 (34.5%)	1,035 (34%)	1,977 (34.7%)	
Race					
White	1,092 (96.4%)	1,458 (96.2%)	2,903 (95.6%)	5,453 (95.9%)	0.2549
Black	29 (2.5%)	41 (2.7%)	100 (3.2%)	170 (2.9%)	
Other	11 (0.9%)	16 (1%)	33 (1%)	60 (1%)	
Histologic type					
Squamous cell carcinoma	320 (28.2%)	434 (28.6%)	406 (13.3%)	1160 (20.4%)	<0.0001
Adenocarcinoma	502 (44.3%)	451 (29.7%)	990 (32.6%)	1,943 (34.1%)	
Small cell carcinoma	47 (4.1%)	202 (13.3%)	627 (20.6%)	876 (15.4%)	
Large cell carcinoma	26 (2.2%)	63 (4.1%)	133 (4.3%)	222 (3.9%)	
Other	237 (20.9%)	365 (24%)	880 (28.9%)	1,482 (26%)	
Comorbidities					
Myocardial infarction	101 (8.9%)	122 (8%)	169 (5.5%)	392 (6.8%)	<0.0001
Congestive heart failure	161 (14.2%)	194 (12.8%)	383 (12.6%)	738 (12.9%)	0.2061
Peripheral vascular disease	114 (10%)	133 (8.7%)	254 (8.3%)	501 (8.8%)	0.0983
Cerebrovascular disease	82 (7.2%)	113 (7.4%)	208 (6.8%)	403 (7%)	0.5543
Dementia	14 (1.2%)	12 (0.7%)	31 (1%)	57 (1%)	0.7232
Chronic pulmonary disease	684 (60.4%)	876 (57.8%)	1,425 (46.9%)	2,985 (52.5%)	<0.0001
Connective tissue disease	39 (3.4%)	32 (2.1%)	60 (1.9%)	131 (2.3%)	0.0103
Peptic ulcer disease	21 (1.8%)	30 (1.9%)	52 (1.7%)	103 (1.8%)	0.6580
Mild liver disease	28 (2.4%)	35 (2.3%)	119 (3.9%)	182 (3.2%)	0.0044
Diabetes without complications	180 (15.9%)	234 (15.4%)	416 (13.7%)	830 (14.6%)	0.0449
Diabetes with complications	24 (2.1%)	17 (1.1%)	25 (0.8%)	66 (1.1%)	0.0009
Paraplegia and hemiplegia	18 (1.5%)	19 (1.2%)	55 (1.8%)	92 (1.6%)	0.4101
Renal disease	78 (6.8%)	81 (5.3%)	169 (5.5%)	328 (5.7%)	0.1728
Moderate or severe liver disease	6 (0.5%)	2 (0.1%)	16 (0.5%)	24 (0.4%)	0.6111

[a]χ^2 tests.

cancer patients, respectively. These numbers are similar to those from hospital-based studies on lung cancer patients with comorbidities. Tammemagi and colleagues (4) conducted a historical cohort study with patients diagnosed between 1995 and 1998 based on patient records, and reported a median survival of 0.86 years (10.32 months). A retrospective chart review in Nebraska conducted by Ganti and colleagues (9) reports a median survival of 8.4 months.

Table 2. Adjusted OR for advanced versus less advanced lung cancer associated with comorbidities

	OR (95% CI)	***P***
Age (ref., 0–44)		
45–54	1.205 (0.781–1.859)	0.3983
55–64	1.075 (0.714–1.618)	0.7306
65–74	0.883 (0.59–1.322)	0.5459
75+	0.987 (0.659–1.478)	0.9482
Race (ref., white)		
Black	1.318 (0.97–1.791)	0.077
Other	0.949 (0.575–1.566)	0.8386
Male vs. female	1.296 (1.17–1.436)	<0.0001
Histology type (ref., adenocarcinoma)		
Large cell	1.668 (1.264–2.202)	0.0003
Small cell	2.879 (2.426–3.415)	<0.0001
Squamous cell	0.646 (0.563–0.741)	<0.0001
Other cell	1.538 (1.348–1.755)	<0.0001
With comorbidities vs. no comorbidities	0.679 (0.602–0.765)	<0.0001

NOTE: All ORs were mutually adjusted for the shown variables in the table.

A national report based on the linked SEER-Medicare database found that the patients with lung cancer had the highest prevalence of comorbidities compared with other cancers; the most prevalent comorbidities were chronic obstructive pulmonary disease (COPD; 33.6%), diabetes (14.7%), congestive heart failure (12.4%), cerebrovascular disease (7.2%), and peripheral vascular disease (6.8%; ref. 16). These are similar to the findings of the present study. The reason for the relatively higher prevalence of COPD in our study could be the use of hospital-based data, where sometimes the occurrence of COPD can be overestimated due to vague descriptions in the medical record (3).

Tammemagi and colleagues (4) found 19 comorbidities that independently predicted survival in lung cancer patients, including infectious diseases, comorbidities with low prevalence (<2%) and specific diseases that were under a more detailed category. Nevertheless, a majority of the comorbidities with relatively high prevalence (>2%) that they found to be significantly associated with poorer survival, that is, congestive heart failure, COPD, liver disease, dementia, and renal disease, were also confirmed by our findings.

We found that diabetes and cerebrovascular disease were negatively associated with survival in patients with regional and distant lung cancer, respectively. Inal and colleagues (17) also found that diabetes was associated with the negative prognostic importance for overall survival, but they only included advanced non–small cell lung cancer patients while controlling

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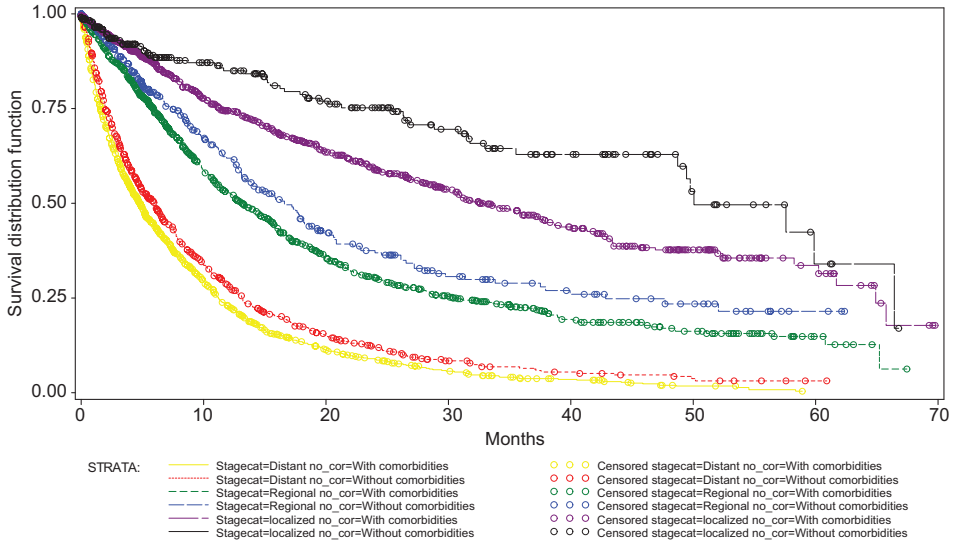

Figure 1.
Survival by stage and comorbidities. As expected, patients with early-stage lung cancer tend to have better survival compared with later stage. Within each stage, patients with comorbidity appear to have poorer survival.

for a limited number of other comorbidities. One explanation for our lack of finding significant associations between diabetes and survival in regional and distant stage lung cancer could be the small sample size of small cell lung carcinoma patients in these two stages (13.3% and 20.6% for regional and distant stage, respectively).

Past studies related to comorbidities and cancer raised two generalized hypotheses: (i) comorbidity was not independently associated with mortality if the index disease was especially lethal and/or the explanatory model used included a number of clinical variables associated with the index diseases (4, 5, 11, 18–21); (ii) the impact of comorbidity is limited to, or predominates in, early-stage diseases (4). Lung cancer is one of the most aggressive forms of cancers with a generally poor prognosis. The first hypothesis was not supported by our findings, as well as another recent study that found negative survival associated with comorbidity after adjusting for cancer stage and histologic type of the cancer (4). The second assumption seemed more plausible, and some even found significant interaction terms between stage and certain comorbidities (4). Interestingly, our finding demonstrating worse outcomes with moderate or severe liver disease (HR, 3.736; 95% CI, 1.088–12.826) and dementia (HR, 2.332; 95% CI, 1.202–4.524) in regional stage lung cancer corresponded to the inconsistent impact of dementia and liver disease on survival across stages found by other studies (4). Renal disease was reported as having a universal impact on survival in both early- and advanced lung cancer in others studies (22), but the impact on early-stage lung cancer was much higher compared with advanced stage lung cancer (HR, 2.74 in early stage;1.42 in advanced stage; 4). In the current study, we also found this kind of change in survival impact for renal disease (regional HR, 1.44; 95% CI, 1.1–1.88; distant HR, 1.11). One reason for this may be related to the use of chemotherapy, which is affected by

Table 3. Multivariate Cox proportional hazards model[a] for overall survival

	Localized	Regional	Distant
	HR (95% CL)	HR (95% CL)	HR (95% CL)
Method 1. Comorbidity as a single variable[a]			
With vs. without comorbidities	1.316 (0.984–1.759)	1.228 (1.037–1.456)	1.075 (0.984–1.174)
Method 2. Comorbidity as 14 individual diseases[a]			
Myocardial infarction	0.713 (0.484–1.052)	0.915 (0.719–1.164)	0.998 (0.839–1.186)
Congestive heart failure	1.731 (1.33–2.253)	1.258 (1.041–1.521)	1.186 (1.05–1.339)
Peripheral vascular disease	0.756 (0.515–1.11)	1.15 (0.903–1.466)	0.962 (0.832–1.112)
Cerebrovascular disease	1.16 (0.8–1.682)	1.161 (0.907–1.487)	1.265 (1.079–1.484)
Dementia	1.211 (0.59–2.485)	2.332 (1.202–4.524)	1.138 (0.785–1.651)
Chronic pulmonary disease	1.184 (0.943–1.485)	1.093 (0.95–1.258)	1.04 (0.959–1.127)
Connective tissue disease	1.156 (0.698–1.915)	1.366 (0.899–2.076)	1.097 (0.834–1.443)
Peptic ulcer disease	1.127 (0.609–2.086)	1.448 (0.948–2.211)	0.992 (0.737–1.336)
Mild liver disease	1.38 (0.602–3.165)	0.847 (0.54–1.328)	0.991 (0.804–1.221)
Diabetes without complications	1.152 (0.878–1.511)	1.016 (0.842–1.227)	0.93 (0.828–1.045)
Diabetes with complications	2.167 (1.122–4.185)	0.688 (0.349–1.356)	0.771 (0.484–1.229)
Paraplegia and hemiplegia	1.688 (0.879–3.243)	1.207 (0.718–2.03)	1.053 (0.77–1.441)
Renal disease	0.808 (0.552–1.184)	1.437 (1.099–1.879)	1.112 (0.935–1.322)
Moderate or severe liver disease	3.736 (1.088–12.826)	1.672 (0.233–11.985)	1.234 (0.752–2.025)

[a]Two methods were used in the multivariate Cox proportional hazard models to assess the effect of comorbidities on the overall survival of lung cancer patients: (i) the overall survival for lung cancer patients with comorbidities compared with those without comorbidities; (ii) the overall survival for lung cancer patients with any one of the 14 particular comorbidities compared with those without such particular comorbidity. In both methods, the analysis was controlled for age, race, sex, and histologic type.

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chemotherapy. Patients with early-stage disease are often treated with either surgery or radiation, whereas those with locally advanced and metastatic disease include chemotherapy (often, platinum-based) as an integral part of their treatment. Because platinum agents are excreted by the kidney, their doses are modified in patients with kidney disease or not used at all (cisplatin). This could at least in part explain the impact of kidney disease on survival in these stages.

In other studies, peripheral vascular disease showed a protective effect against mortality, which can plausibly be explained by anticoagulants used in the treatment of peripheral vascular disease are also used to inhibit cancer progression and metastasis (4, 23, 24). Although we found that patients with peripheral vascular disease were associated with a lower risk of death (localized HR, 0.76; 95% CI, 0.52–1.11; Distant HR, 0.96; 95% CI, 0.83–1.11), the results were not significant.

The association between comorbidity and lung cancer survival is clinically plausible as the deleterious effects of most of the comorbid conditions can diminish the function of vital organs systems and may compromise treatment directly or through their association with other comorbidities (4). Patients with comorbidities may be diagnosed at an earlier stage due to more surveillance and screening given their frequency of clinician visits (3, 25–28). Our study supported this hypothesis as having any comorbidities was significantly associated with lung cancer diagnosed at an earlier stage ($P < 0.0001$) after controlling for age, race, gender, and histologic subtype.

Congestive heart failure (CHF) was associated with survival across all stages of lung cancer in our population. One study mentioned that congestive heart failure can indirectly impact survival because of its association with nonreceipt of cancer treatment (4). Patients with congestive heart failure were found significantly less likely to receive surgery or chemotherapy than patients without CHF (29). This partially explained why CHF has greater impact on localized stage lung cancer (HR, 1.731) compared with its decreased impact in regional stage (HR, 1.258) and distant stage (HR, 1.186) since the decision to proceed with surgery, the treatment of choice in this stage is affected by the presence or absence of CHF. Other comorbidities, such as dementia, renal, and liver diseases, are likely to be both associated with other comorbidities and nonreceipt of cancer treatment.

Our study population is slightly older than reported by other studies (3). An older population probably contributed to a higher proportion of patients with comorbidities: 73.3% of the patients in our population had comorbidities of interest compared with 66% in the aforementioned study. The number of people with comorbidities in the present study is also higher than the national numbers based on SEER-Medicare data on patients ages >65 years (16), which reported a 52.9% of the patients with some comorbidities. Although this number may vary depending on the definition of comorbidities in different studies, the high proportion of patients with comorbidities seen here could also be because of data source utilized. The hospital discharge data, based on which we identified comorbidities, could possibly have captured more patients with comorbidities than using data collected from Medicare claims data.

One limitation of this study is that smoking status was not controlled in this study due to the inaccuracy in recording smoking status using administrative data. Future studies need to overcome this weakness and clarify the role played by smoking in the model examining the comorbidities when controlling for other demographic and clinical variables. The number of comorbidity conditions studied here is also limited. Considerations should be given to other diseases when modeling the survival in lung cancer patients.

The comorbid conditions in this study were identified in the HDD at the time of diagnose (based on NCR). It is possible that we did not manage to catch all of the precomorbidity that might show up in pervious hospital admission before lung cancer diagnosis. However, the comorbidity conditions that we were interested in were mostly chronic conditions. If some conditions were not recorded in the diagnostic codes at the first cancer-diagnosis admission, there is a high probability that the conditions were either transient or already cured by the time lung cancer was diagnosed.

For concurrent comorbidities or those effects of cancer, unfortunately, we were unable to rule them out completely. This is one of the difficulties when conducting comorbidity research using historical data. Our goal is to compare the outcomes in patients with/without certain comorbidities, and to look at the overall survival given the conditions of the patients. It is not our intention to disentangle the causal relationship between comorbidity and lung cancer outcomes, which may interact with each other through a variety of mechanism as we mentioned before, and the investigation of which could be better accomplished using cancer/non–cancer-specific death adjusted for treatment.

During the follow-up of this study, 1,145 (20.1%) patients got censored after less than 1 year of the follow-up period, which can be considered as stop-of-contact/loss-to-follow-up in this study, though The NDHHS has been managing high-quality cancer registry database being awarded Gold Certification for data quality by the North American Association of Central Cancer Registries (NAACCR) each year. However, when comparing the hazards of death between patients with and without comorbidities, we tried our best and keep the informative censoring to a minimum by utilizing both the censored and uncensored data points in the Cox proportional hazard model to draw a more convincing and comprehensive conclusion on the additional magnitude of the survival risk due to comorbidities. The Cox proportional hazard model uses the survival time of the censoring data, which provides a much more accurate estimation comparing with logistic regression or maximal likelihood estimate, which only utilized the uncensored subjects. We provided the 1-year survival so that our study can be compared with studies that used administrative datasets alike, but we put much more emphasis on the additional magnitude of the survival risk contributed to individual comorbid conditions.

Given the comparatively high quality of the original databases and the linkage (13), there were still 20.1% patients that were censored after less than 1 year of the follow-up period. To better avoid underestimation and overestimation of our 1-year survival proportions, we exclude these patients who are censored within one year, but patients who are censored after one year were included in the 1-year survival calculation.

In order to achieve enough number of lung cancer patients at certain stages with different types of comorbid conditions, small cell and non–small cell lung cancer patients were analyzed together and adjusted for histologic types in the model. In the future, we would continue to study comorbid conditions in these two types of lung cancer separately because their behavior and

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treatment were different. Analyzing small cell and non–small cell lung cancer can also avoid treating histologic type as a confounding effect when using it as a variable in the model.

Overall, the results of this study will contribute to a better understanding of how various comorbid conditions affect survival in lung cancer. The use of population-based cancer registry linked with hospital discharge data in this study allows large sample size, extensive variables, and wide array of comorbidities to be studied.

The nature of any study evaluating the impact of comorbidity in cancer is that the causal relationships of these associations between different comorbidities and survival are multifaceted and interact with each other through multiple mechanisms. The relationship between the existence of comorbidity and receipt of treatment, as well as the interference of comorbid conditions on staging need to be further elucidated through population cohort and experimental studies. These findings hopefully will be beneficial to guide the treatment and management of comorbid conditions in lung cancer patients, to enhance more intensive monitoring and appropriate treatment.

Our conclusion is that after adjusting for age, race, sex, stage, and histology, different comorbid conditions were significantly associated with lung cancer survival at different stages. Future models for predicting lung cancer survival should take individual comorbid conditions into consideration, and a new comorbidity index should be developed with emphasize on the different effects of some specific comorbidities.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: K.M.M. Islam, G. Lin, A.K. Ganti
Development of methodology: K.M.M. Islam, X. Jiang, G. Lin, A.K. Ganti
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): G. Lin, A.K. Ganti
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): K.M.M. Islam, X. Jiang, G. Lin, A.K. Ganti
Writing, review, and/or revision of the manuscript: K.M.M. Islam, X. Jiang, T. Anggondowati, G. Lin, A.K. Ganti
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): K.M.M. Islam, G. Lin
Study supervision: G. Lin, A.K. Ganti

Disclaimer

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