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ORIGINAL PAPER

Comorbidity and stage at diagnosis among lung cancer patients in the US military health system

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Abstract

Purpose We investigated the association between comorbidities and stage at diagnosis among NSCLC patients in the US Military Health System (MHS), which provides universal health care to its beneficiaries.

Methods The linked data from the Department of Defense's Central Cancer Registry (CCR) and the MHS Data Repository (MDR) were used. The study included 4768 patients with histologically confirmed primary NSCLC. Comorbid conditions were extracted from the MDR data. Comorbid conditions were those included in the Charlson Comorbidity Index (CCI) and were defined as a diagnosis during a 3-year time frame prior to the NSCLC diagnosis. Multivariable logistic regression was performed to estimate odds ratios (ORs) and 95% confidence intervals (95% CI) of late stage (stages III and IV) versus early stage (stages I and II) in relation to pre-existing comorbidities.

Results Compared to patients with no comorbidities, those with prior comorbidities tended to be less likely to have lung cancer diagnosed at late stage. When specific comorbidities were analyzed, decreased odds of being diagnosed at late stage were observed among those with chronic obstructive pulmonary disease (COPD) (adjusted OR 0.78, 95% CI 0.68 to 0.90). In contrast, patients with a congestive heart failure or a liver cirrhosis/chronic hepatitis had an increased likelihood of being diagnosed at late stage (adjusted OR 1.30, 95% CI 1.00 to 1.69 and adjusted OR 1.87, 95% CI 1.24 to 2.82, respectively).

Conclusions Among NSCLC patients in an equal access health system, the likelihood of late stage at diagnosis differed by specific comorbid diseases.

Keywords Lung cancer · Cancer stage · Comorbidity · Universal health care · Military health system

Introduction

Cancer stage at diagnosis is an important determinant of survival [1–3]. Stage may be affected by multiple factors, including comorbidities [4–7]. People with and without a comorbid condition may differ in seeking and receiving health care and therefore differ in the detection and diagnosis of cancer.

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The effects of pre-existing comorbidities on cancer stage at diagnosis can be complex [8–10]. On the one hand, due to more frequent medical visits and increased disease surveillance, cancer patients with pre-existing comorbidities may be more likely to have cancer diagnosed earlier, supporting the "surveillance hypothesis" [8, 11]. On the other hand, there is "competing demand hypothesis" [11, 12], in which comorbidities may be associated with later stage at diagnosis because physicians and patients may not give timely attention to sites other than that where the comorbidity occurs. As a result, early signs or symptoms of cancer at the site other than the cancer site may be masked by symptoms of comorbidity and cancer diagnosis may be thus delayed.

Lung cancer is the leading cause of cancer-related death in the US with 57% patients diagnosed at late stages [13]. Non-small cell lung cancer (NSCLC) comprises 85–90% of all lung cancers [13]. More than 70% of NSCLC patients have at least one comorbidity [14]. Although comorbidity has been extensively studied for its impact on survival and treatment receipt among lung cancer patients [15–21], the relationship between comorbidity and stage at lung cancer diagnosis has been seldom investigated. Among a few published studies, comorbidity was studied based on whole disease burden index only [22, 23] or surrogate measure [24], with no studies examining whether cancer stage at diagnosis may differ by specific comorbid conditions. Furthermore, previous studies were usually conducted in populations in which stage at diagnosis was affected by health care access (i.e., persons with poor access to care might be more likely to be diagnosed at later stages) and therefore affect the assessment of the relationship between the two.

The US military health system (MHS) provides universal health care to military personnel, retirees, and their family members. Beneficiaries have no financial barriers to receive health care, which minimizes the potential effects of access to health care on diagnosis of both comorbidities and NSCLC. Therefore, a study performed in the MHS could provide more solid evidence on the relationship between comorbidities and NSCLC stage at diagnosis, compared to studies in the general populations. The aim of this study was to investigate the relationship between comorbidities and stage at diagnosis among NSCLC patients in the US Military Health System (MHS).

Materials and methods

Data sources

The linked database from the Department of Defense (DoD)'s Central Cancer Registry (CCR) and the MHS Data Repository (MDR) was used for this study and described previously [25, 26]. The MDR contains data on inpatient and outpatient care provided at military treatment facilities MTFs and civilian facilities paid for by the DoD, including information on clinical diagnoses of all medical conditions, which are coded using the International Classification of Disease, 9th Revision (ICD-9), and diagnostic and treatment procedures, which are coded using ICD-9 or Current Procedural Terminology (CPT) codes. The CCR contains information on MHS beneficiaries with cancer who had ever diagnosed and/or treated at military treatment facilities (MTFs). The CCR Data include demographic variables, cancer diagnosis, treatment, recurrence, and vital status. Cancer site and histology codes are based on the International Classification of Diseases for Oncology, third edition (ICD-O-3) [27]. Tumor stage was defined as derived stages I–IV according to the American Joint Committee on Cancer (AJCC) staging system, the 7th edition [28]. Quality assurance was conducted following the guidelines established by the North America Association of Central Cancer Registries. The data linkage project was approved by the Institutional Review Boards of the Walter Reed National Military Medical Center, TRICARE Management Activity, and the National Institutes of Health Office of Human Subjects Research.

Study population

The study subjects were patients ($N=5{,}054$) diagnosed with histologically confirmed primary NSCLC between 1998 and 2007, identified from the CCR. Patients identified The cancer site and histology were classified using the topography (C34.0 to C34.3, C34.8, C34.9) and morphology codes (8050–8078, 8083, 8084, 8250–8260, 8480–8490, 8570–8574, 8140, 8211, 8230, 8231, 8323, 8550, 8551, 8576, 8010–8012, 8014–8031, 8035, 8310, and any other NSCLC codes between 8010 to 8576) of the International Classification of Diseases for Oncology, third edition (ICD-O-3) [27].

Comorbidity conditions

Comorbidity data were obtained from the MDR. Comorbidities were those as included in the Charlson Comorbidity Index (CCI) [29]. Except for the comorbidity "metastatic solid tumors" which did not occur in the study population, all other specific comorbidities were used to calculate the CCI index. Dementia, moderate or severe liver disease, diabetes with complications, and acquired immune deficiency syndrome were not included in the analysis of specific comorbidities due to the small numbers of patients for certain cancer stages. The specific comorbidities included were myocardial infarction, congestive heart failure, peripheral vascular diseases, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), rheumatologic disease, ulcer disease, mild liver disease, diabetes without

complications, paraplegia and hemiplegia, renal disease, and cancers other than lung cancer. Comorbidities were identified based on at least one inpatient record or three or more outpatient records using ICD-9 or CPT codes, [30, 31] and defined as having the diagnosis during the 3-year period before NSCLC diagnosis. Literature is not consistent in the time frame from comorbidity to cancer diagnosis (ranging from 1 to 10 years [9, 16, 22, 32]). We chose the 3-year time frame to be in line with the majority of literature.

Statistical analyses

The outcome of this study was NSCLC stage at diagnosis. Stage was further grouped into early stage (stages I and II), [33, 34] and late stage (stages III and IV) [35]. A total of 286 (5.6%) patients were excluded due to unknown or missing stage information.

We first described the distributions of demographic, diagnostic, treatment, and other variables by stage using χ^2 test. Multivariable logistic regression was performed to estimate odds ratios (ORs) and 95% confidence intervals (95% CI) of comorbidities in relation to cancer stage at NSCLC diagnosis. ORs of comorbidities were estimated for late stage vs. early stage. We first assessed tumor stage in relation to the CCI [29] which was grouped into four groups based on index score of 0, 1, 2, ≥ 3, respectively. We then assessed stage in relation to specific comorbidities.

Results

A total of 4768 patients were included in the final analysis. Patient characteristics by stage at diagnosis are shown in Table 1. There were significant differences in age, gender, race, marital status, tobacco use, and histology between early (stages I and II) and late stage (stages III and IV) patients. Compared to patients with early-stage cancer, those with late-stage cancer tended to be younger ($p < 0.001$) and more likely to be male ($p < 0.001$), never married ($p = 0.034$), and current tobacco user ($p = 0.006$). They were less likely to be White or Asian ($p = 0.010$), and less likely to have squamous cell carcinoma or adenocarcinoma than those with early-stage tumors ($p < 0.001$).

Table 2 shows the adjusted odds ratios for the relationship between tumor stage and comorbidity. Compared to patients with a CCI of 0, those with a CCI of 1, 2, and 3 or more exhibited borderline decreased odds of being diagnosed with late stage. The adjusted ORs for those with a CCI of 1, 2, and 3 were 0.88 (95% CI 0.75–1.02), 0.89 (95% CI 0.74–1.06), and 0.87 (95% CI 0.74–1.03), respectively. However, the reduced odds of having a late-stage cancer diagnosis were only present among patients with COPD (adjusted OR 0.78, 95% CI 0.68 to 0.90). In contrast, among patients with congestive heart failure, there was an increased likelihood of being diagnosed at late stage (adjusted OR 1.30, 95% CI 1.00 to 1.69). Likewise, cirrhosis/chronic hepatitis was associated with increased likelihood of late-stage diagnosis (adjusted OR 1.87, 95% CI 1.24 to 2.82).

Discussion

Our study found that, among NSCLC patients in an equal access health system, the likelihood of late stage diagnosis differed by specific comorbid diseases, although overall there was a suggestive deceased likelihood of late-stage diagnosis among patients with comorbidities than those without. Patients with COPD were less likely to be diagnosed with a later stage while patients with congestive heart failure or cirrhosis had a higher chance of being diagnosed with late-stage cancer. We used a 3-year time frame to identify comorbidities that were diagnosed before lung cancer.

Compared to the vast majority of literature on comorbidity in relation to lung cancer survival, the relationship between comorbidity and lung cancer stage at diagnosis has been understudied. In general, the limited studies displayed a positive association between earlier stage and higher comorbidity burden [22–24], supporting the "surveillance hypothesis," which states that patients with coexisting disease would be more likely to have "increased frequency of medical visits and therefore have a greater opportunity for early cancer diagnosis." [11]. Consistent with our findings, in a large study of more than 50,000 patients from the SEER population [24], NSCLC patients with comorbidity disorders, as defined by having Social Security Disability Insurance (SSDI) entitlement in Medicare, had lower odds for late-stage NSCLC diagnosis (OR 0.76, 95% CI 0.72 to 0.81) than people without SSDI coverage after adjusting for age, sex, race/ethnicity, marital status, geographic region, and year of diagnosis. In a study based on the data from multiple hospital registries in Texas, Ahn et al. 2013 found that NSCLC patients with a higher Charlson Comorbidity Index (CCI) were significantly more likely to present with early stage (stage I and II) than were patients with lower CCI [23]. More frequent medical care and closer clinical monitoring received by patients with more comorbidities and those with disabilities were explained as possible reasons for early detection of lung cancer [23, 24]. In line with these observations, results from the Danish Lung Cancer Registry showed significantly decreased odds of advanced-stage diagnosis with higher comorbidity burden after adjusting for multiple covariates including age, gender, education level, and income (adjusted OR 0.73, 95% CI 0.65 to 0.81) [22]. Interestingly, in stratified analysis, opposite to the overall results, men without employment were more likely to be

Table 1 Demographic characteristics by stage at diagnosis among non-small-cell lung cancer patients ($N=4768$) diagnosed from 1998 to 2007 in the military health system

Demographic variables	Early stage ($N=2,068$) Number (%)	Late stage ($N=2,700$) Number (%)	p-value
Age			< 0.001
< 50	109 (5.27)	230 (8.52)	
50–59	338 (16.34)	527 (19.52)	
60–69	832 (40.23)	1,004 (37.19)	
70–79	614 (29.69)	725 (26.85)	
80 and older	175 (8.46)	214 (7.93)	
Sex			< 0.001
Male	1,273 (61.56)	1,817 (67.30)	
Female	795 (38.44)	883 (32.70)	
Race			0.010
White	1,684 (81.43)	2,130 (78.89)	
Black	226 (10.93)	323 (11.96)	
Asian	100 (4.84)	70 (2.59)	
Other	54 (5.61)	153 (5.67)	
Unknown or missing	4 (0.19)	24 (0.89)	
Marital status			0.034
Never married	51 (2.47)	98 (3.63)	
Married	1,563 (75.58)	2,004 (74.22)	
Separated or divorced	112 (5.42)	178 (6.59)	
Widowed	277 (13.39)	324 (12.00)	
Unknown or missing	65 (3.14)	96 (3.56)	
Sponsor service branch			0.126
Army	735 (35.54)	986 (36.52)	
Navy	404 (19.54)	486 (18.00)	
Air force	691 (33.41)	914(33.85)	
Marines	80 (3.87)	91 (3.37)	
Coast guard	20 (0.97)	13 (0.48)	
Other, unknown or missing	138 (6.67)	210 (7.78)	
Active duty status			0.058
No	1,989 (96.18)	2,604 (96.44)	
Yes	53 (2.56)	79 (2.93)	
Unknown or missing	26 (1.26)	17 (0.63)	
Tobacco use			0.006
Never used	169 (8.17)	188 (6.96)	
Previous use	1,096 (53.00)	1,364 (50.52)	
Current use	660 (31.91)	987 (36.56)	
Unknown or missing	143 (6.91)	161 (5.96)	
Histology			< 0.001
Squamous cell carcinoma	579 (28.00)	624 (23.11)	
Adenocarcinoma	1,060 (51.26)	1,116 (41.33)	
Large cell carcinoma	144 (6.96)	326 (12.07)	
Other	285 (13.78)	634 (23.48)	
Charlson Comorbidity Index			0.06
0	944 (45.65)	1,339 (49.59)	
1	457 (22.10)	548 (20.30)	
≥ 2	288 (13.93)	359 (13.30)	
≥ 3	379 (18.33)	454 (16.81)	

Table 2 The association between comorbidities and stage at diagnosis among non-small-cell lung cancer patients diagnosed from 1998 to 2007 in the military health system

Comorbidities	Late stage vs. early stage	
	No. (early/late)	Adjusted OR (95% CI)*
Charlson Comorbidity Index		
0	944/1,339	1.00 (ref)
1	457/548	0.88 (0.75–1.02)
2	288/359	0.89 (0.74–1.06)
≥ 3	379/454	0.87 (0.74–1.03)
Myocardial infarction		
No	1,916/2,537	1.00 (ref)
Yes	152/163	0.79 (0.62 to 1.02)
Congestive heart failure		
No	1,932/2,507	1.00 (ref)
Yes	136/193	1.30 (1.00 to 1.69)
Peripheral vascular disease		
No	1,827/2,432	1.00 (ref)
Yes	241/268	0.91 (0.74 to 1.13)
Cerebrovascular disease		
No	1,901/2,512	1.00 (ref)
Yes	167/188	0.91 (0.71 to 1.15)
Chronic obstructive pulmonary disease		
No	1,501/2,082	1.00 (ref)
Yes	567/618	0.78 (0.68 to 0.90)
Rheumatologic disease		
No	2,005/2,640	1.00 (ref)
Yes	63/60	0.82 (0.57 to 1.18)
Ulcer disease		
No	2,035/2,647	1.00 (ref)
Yes	33/53	1.32 (0.84 to 2.08)
Mild liver disease/cirrhosis/chronic hepatitis		
No	2,034/2,613	1.00 (ref)
Yes	34/87	1.87 (1.24 to 2.82)
Diabetes without complications		
No	1,727/2,240	1.00 (ref)
Yes	341/460	1.05 (0.89 to 1.24)
Paraplegia and hemiplegia		
No	2,058/2,686	1.00 (ref)
Yes	10/14	1.02 (0.44 to 2.35)
Renal disease		
No	2,008/2,618	1.00 (ref)
Yes	60/82	1.03 (0.72 to 1.48)
Other cancers		
No	1,794/2,391	1.00 (ref)
Yes	274/309	0.88 (0.73 to 1.05)

OR odds ratio, *CI* confidence interval

*Adjusted for age, sex, race, active duty status, tobacco use, and histology. Specific comorbidities were also mutually adjusted

diagnosed with advanced stage even at higher comorbidity burden, indicating that these men might be less likely to receive surveillance than employed people despite having more comorbidities [22]. This finding suggested that a precondition of the "surveillance hypothesis" is accessibility to medical care. In the studies mentioned above, patients had Medicare coverage [24], national health insurance coverage [22], or were enrolled in a primary safety net health care

system [23], which made the surveillance of comorbid diseases possible. All patients in our study had universal health insurance as beneficiaries of the US MHS.

Apart from the association between overall comorbidity and stage, the variation in the association for different comorbid conditions is noteworthy. However, in previous studies, either no analyses were performed by specific comorbid condition [22, 24], or only COPD was studied to the best of our knowledge [23]. It is not surprising that patients with COPD were specifically more likely to be diagnosed at earlier stage of lung cancer under the "surveillance hypothesis." Frequent medical care and closer clinical monitoring, especially X-rays or CT scans that were used for patients with compromised lung function, may help detect lung cancer at earlier stages in these patients [22]. Since COPD is an established risk factor for lung cancer, [36] patients with prior COPD may be under more intensive surveillance and their medical providers may be more likely to apply these examinations so that lung cancer could be diagnosed at an earlier stage. On the other hand, the association with tumor stage differed for comorbidities in organs other than the lung. An increased likelihood of being diagnosed at late stage among patients with congestive heart failure and cirrhosis may be consistent with the "competing demand hypothesis," which suggests that due to the management of comorbid disease, physicians and patients may not give timely attention to cancers at other sites and therefore cancer diagnosis may be delayed [11, 12]. For example, for patients with congestive heart failure, symptoms related to both lung cancer and heart disease, such as shortness of breath, could be overshadowed by the attention to heart disease, thus delayed the diagnosis of lung cancer.

In addition to the "competing demand hypothesis" and the "surveillance hypothesis" discussed above, differences in health care utilization by disease types, duration and severity, as well as the differences in disease management could also affect cancer diagnosis [37]. These hypotheses need to be investigated for lung cancer since no studies on specific comorbidities other than COPD and lung cancer stage have been conducted to the best of our knowledge, although there have been studies in breast cancer [8–10], prostate cancer [38], and colorectal cancer [8, 10]. Literature also suggested other hypotheses regarding the complex relationship between specific comorbidities and cancer stage [8, 9, 11]. For cancers with standard screening available, such as breast cancer, mammography may have modification effects on the relationship between comorbidity and stage [32]. Our data for this study covered the period when lung cancer screening was not available. Future analysis stratified by time periods (e.g., before and after when lung cancer screening was recommended) would provide further information on the relationship between comorbidities and lung cancer stage at diagnosis.

Our study has the strength of utilizing the large DoD CCR and MDR linked database, which allowed stratified analysis of specific comorbidities, although the numbers of some comorbidities were still small. Moreover, the equal access to health care in the DoD health care system may reduce potential confounding by factors related to health care access. However, there are other factors that cannot be controlled in the study might have affected the results. For example, variation in health care utilization or management could impact cancer stage at diagnosis, depending on type, duration, and severity of a comorbid condition [37]. Although we studied the effect of disease type, the impacts of disease duration and severity warrant further study. This study was also limited in including only comorbidities as defined in the CCI. Other comorbidities, especially those frequently co-occur with lung cancer, should be investigated in future research. This study included patients from 1998 to 2007, a period of time before widespread recommendations for lung cancer screening. Further analyses are needed to ascertain whether the findings in this study persist into the lung cancer screening era. Despite these limitations, our analysis of a large cohort of patients with lung cancer in this equal access system further defines the association of stage at diagnosis with comorbidities.

In conclusion, our study suggested that in an equal access system, although NSCLC patients with comorbidity exhibited lower odds of being diagnosed at a later stage than patients without comorbidity, stage at diagnosis differed by specific comorbid diseases. Future studies are needed to further explore the effects of specific comorbid conditions on tumor stage at diagnosis among NSCLC patients.

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