Original Article

Depression and Health Care Utilization at End of Life Among Older Adults With Advanced Non–Small-Cell Lung Cancer

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Abstract

Context. Limited data exist regarding how depression diagnosed at different times relative to a cancer diagnosis may affect healthcare utilization at end of life (EOL).

Objectives. To assess the relationship between depression and health care utilization at EOL among older adults (ages >=67) diagnosed with advanced non-small cell lung cancer (NSCLC) from 2009 to 2011.

Methods. Using the SEER-Medicare database, we fit multivariable logistic regression models to explore the association of depression with duration of hospice stay plus high-intensity care, for example inpatient admissions, in-hospital death, emergency department visits, and chemotherapy at EOL. We used a regression model to evaluate hospice enrollment, accounting for the competing risk of death.

Results. Among 13,827 subjects, pre-cancer depression was associated with hospice enrollment (sub-hazard ratio 1.19, 95% confidence interval [CI] 1.11–1.28), 90 + hospice days (adjusted odds ratio [aOR] 1.29, 95% CI 1.06–1.58), and lower odds of most utilization; we found no association with EOL chemotherapy. Diagnosis-time depression was associated with hospice enrollment (SHR 1.16, 95% CI 1.05–1.29) but not high-intensity utilization. Post-diagnosis depression was associated with lower hospice enrollment (SHR 0.80, 95% CI 0.74–0.85) and higher odds of ICU admission (aOR 1.18, 95% CI 1.01–1.37).

Conclusion. EOL healthcare utilization varied by timing of depression diagnosis. Those with pre-cancer depression had lower odds of high-intensity healthcare, were more likely to utilize hospice, and have longer hospice stays. Regular depression screening and treatment may help patients optimize decision-making for EOL care. Additionally, hospice providers may need additional resources to attend to mental health needs in this population. J Pain Symptom Manage 2018;56:699–708.

Key Words

Lung neoplasms, depression, hospice care, palliative care

Introduction

Non-small cell lung cancer (NSCLC) is a highly lethal cancer that largely affects older adults, many of whom have multiple comorbidities and high symptom burden.[1,2] Depression is prevalent among older adults with lung cancer,[3,4] as depression is associated with both increased age and comorbidities. The presence of depression negatively affects quality of life for patients with lung cancer[5] and decreases survival among those with advanced disease.[6]

Patients with cancer and depression have longer hospital stays and more readmissions[7] compared to cancer patients without depression,[8,9] High intensity

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end-of-life (EOL) care, such as hospitalization, emergency department (ED) visits, and chemotherapy use, is associated with poorer quality of life for cancer patients[10] and their surviving caregivers,[11] does not confer a survival benefit,[12,13] and is often discordant with the preferences of most cancer patients who would prefer to die at home or without high-intensity interventions.[14,15] While hospice is a reasonable recommendation for patients with advanced cancer[16] as an alternative to high-intensity healthcare, study findings have been mixed regarding the association between psychological distress and hospice enrollment.[17,18]

While depression may affect decision making, which in turn affects the quality of care received, no studies have explored the association between depression noted at different times relative to a cancer diagnosis and EOL healthcare utilization. While pre-cancer depression is not modifiable by clinicians, patients presenting with a history of depression have poorer functional status, more depressive episodes, and may have treatment-resistant depression, all of which negatively affects patient outcomes.[19] Knowing if depression that manifests at different times is associated with the intensity of EOL healthcare utilization can help with the timing of depression screening as well as potential interventions to maximize patients' decision-making capabilities in the face of life-limiting illness. Herein, we explored the association between pre-cancer, diagnosis-time, or post-diagnosis depression and EOL care received in a population-based sample of older adults with advanced NSCLC. We hypothesized that individuals with pre-cancer depression, given their longer history of distress and symptom burden, were least likely to use hospice and most likely to use high-intensity healthcare interventions at end of life.

Patients and Methods

Study Population

We used the SEER-Medicare database, comprised of Medicare claims linked to clinical data for subjects in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) dataset. The clinical records of 94% of subjects 65 and older in the SEER registries are connected to Medicare claims, with the demographic distribution in the database reflecting the population of older adults in the United States.[20] We included subjects age 67+ with NSCLC diagnoses from 2009 to 2011 and Medicare claims spanning 2007–2013. These inclusion criteria allowed for a look-back period of 24 months prior to NSCLC diagnosis to note depression claims and to evaluate Part D claims for oral chemotherapy.

To evaluate EOL decision-making within the timeframe of available claims, we limited our evaluation to subjects with metastatic (stage IIIB or IV) NSCLC diagnoses staged per American Joint Committee on Cancer (AJCC) sixth edition, given the limited life expectancy of this population. Staging histology codes appear in the Appendix. While guidelines recommend chemotherapy receipt in this population,[21] a previous analysis has noted that among older adults with metastatic NSCLC, approximately 50% received no surgery, radiation or chemotherapy.[22] As we cannot review patient and clinician preferences in claims data, hospice is a reasonable choice given the limited life expectancy of this cohort, and our focus is EOL care, we evaluated time to hospice enrollment and hospice duration rather than receipt of chemotherapy, surgery or radiation. Additionally, as anti-cancer therapies affect survival following an advanced lung cancer diagnosis,[23] and we purposefully did not evaluate these therapies, we did not perform survival analyses.

We required that all subjects had continuous enrollment in fee-for-service Medicare parts A and B for at least 24 months prior to diagnosis to calculate a comorbidity score and evaluate for pre-cancer depression. We excluded patients diagnosed at autopsy or by death certificate and those diagnosed with other cancers or primary occult/unknown stage cancer. We also omitted subjects enrolled in a managed care plan, people who did not incur claims prior to their NSCLC diagnosis and people who qualified for Medicare based on end-stage renal disease. We eliminated records for subjects with claims for bipolar disorder or schizophrenia. We excluded subjects who did not die during the study observation period for our evaluation of inpatient admissions, intensive care unit (ICU) admissions, and ED visits in the last month of life, and chemotherapy receipt in the last 14 days of life. Our study criteria and resulting population appear in Figure 1. The Institutional Review Board of the Fred Hutchinson Cancer Research Center approved this study.

Measures of Healthcare Utilization

The goal of our analysis is to describe the association between depression, hospice use, and high-intensity healthcare utilization at end of life. Using previously published metrics, we defined high-intensity EOL care as chemotherapy in the last 14 days of life; less than 3 days of hospice use or no hospice use; any ICU admission, >1 hospitalization, in-hospital death, or >1 ED visit in the last 30 days of life.[24-26] We evaluated length of hospice enrollment, as longer hospice stays are associated with higher benefits to families and patients.[27,28] We searched the inpatient, outpatient, carrier, and hospice claims files for hospitalization, ICU admission, in-hospital death (recorded as discharge status on claims), ED visits,

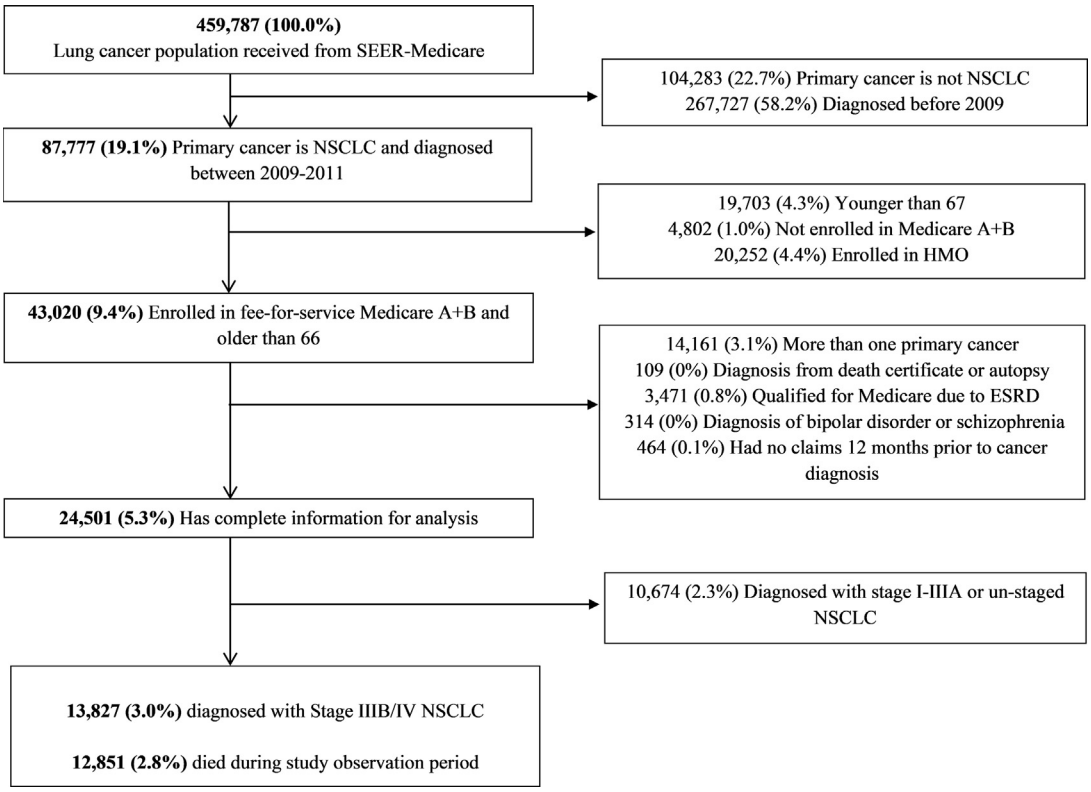

Fig. 1. Consort diagram for study population.

and hospice use, with claim start dates used to calculate receipt of services relative to recorded death date. We searched for chemotherapy claims using Healthcare Common Procedure Coding System (HCPCS) for chemotherapy medications and administration in inpatient, outpatient, and durable medical equipment claims files, plus name search in Part D claims for oral chemotherapy or targeted therapies. We searched for systemic medications recommended for metastatic NSCLC per National Comprehensive Cancer Network guidelines available in 2012–2013, the last year of available claims.[21]

Definition of Depression

We used a previously published algorithm that compared concordance between clinical diagnoses of depression and Medicare claims for older patients to identify patients with depression claims.[29] We looked for International Classification of Disease, version 9 (ICD-9) codes 296.2, 296.3, 298.0, 300.4, 309.0, 309.1, or 311 in inpatient, outpatient, and carrier claims files in the two years prior to and all claims after each patient's NSCLC diagnosis date. Additionally, we searched for any claims with the HCPCS codes G8431or G8511 indicating a positive depression screen, with or without documented treatment plan.

We categorized subjects into one of four categories: pre-cancer depression, diagnosis-time depression, post-diagnosis depression, or no depression. If a subject had a claim with an ICD-9 code or HCPCS code indicating depression in the 3 to 24 months preceding the NSCLC diagnosis, then we classified the subject as having pre-cancer depression. We characterized patients with a first depression code appearing in the 3 months preceding diagnosis to 30 days following diagnosis as having diagnosis-time depression,[30-33] as 3 months is a typical timeframe between symptom lead-time and an NSCLC diagnosis. We classified subjects with depression claims that first appeared more than 30 days after the NSCLC diagnosis date as having post-diagnosis depression.[34,35] The comparator group had no claims for depression at any time.

Covariates

Through a literature search, we identified factors that may affect EOL healthcare utilization and outcomes for patients with NSCLC and/or depression. As race,[36] Hispanic ethnicity,[37] gender,[38] age,[38] socioeconomic status,[39] marital status,[40] and rural residence[36] have been identified as affecting healthcare utilization and patient outcomes, we controlled for these covariates in multivariable logistic regression models and competing risk regression. As many people with depression also experience anxiety,[41] which may also affect EOL decision making,[18] we controlled for anxiety among subjects using claims noting anxiety

disorder.[42] To control for possible geographic differences in healthcare utilization at EOL,[43,44] we controlled for SEER registry, grouping registries as follows: West (San Francisco, San Jose, Los Angeles, Greater California, Hawaii, New Mexico, Seattle, Utah), Midwest (Detroit, Iowa), South (Atlanta, rural Georgia, Kentucky, Louisiana), and Northeast (Connecticut, New Jersey). For comorbidity calculations, we used the National Cancer Institute composite (Klabunde-Charlson) comorbidity index.[45,46] Subjects without any claims for depression comprised the control group.

Statistical Analyses

We calculated descriptive statistics for subjects with and without a history of depression with respect to age at diagnosis, gender, marital status, race, Hispanic ethnicity, comorbidity index, SEER registry, Medicaid eligibility, and urban residence.

To characterize the association between depression and hospice enrollment, we conducted a competing risk regression, accounting for the competing risk of death.[47,48] We included all subjects diagnosed with NSCLC, regardless of whether we observed the subject's death during the study period. We censored patients not observed to die by the end of the claims observation period of December 31, 2013. We describe duration of hospice enrollment, and constructed multivariable logistic regression models to determine the odds of very short hospice enrollment (<3 days) or lengthy hospice enrollment (longer than 90 days) by depression category.

To evaluate EOL healthcare utilization, we excluded subjects who did not die during the study period so we had the chance to observe the outcomes of interest. Among the remaining study population of decedents, we constructed multivariable logistic regression models to determine odds of in-hospital death, >1 ED visits, >1 hospitalizations, or ICU admission in the last 30 days of life, or chemotherapy receipt in the last 14 days of life. We controlled for days survived following diagnosis and demographic covariates. Initially, we included interaction terms for gender and age given the different incidence in depression by gender and age, however these were not in our final models as the interaction terms were not statistically significant.

We adjusted for the aforementioned covariates in all regression models and performed all analyses using Stata statistical software, version 15.1 (StataCorp, College Station, TX).

Sensitivity Analysis

We performed two sensitivity analyses. First, in our logistic regression models we excluded patients who did not survive 30 days following diagnosis to determine how the exclusion of such patients affected our results. Next, using a claims-based algorithm to identify subjects with a smoking history, we created a covariate to control for smoking in this cohort.[49] We included this covariate in our regression models to evaluate how attempting to control for smoking status in our analyses affected results, as smoking affects patient outcomes[50] but smoking status is not available in the SEER-Medicare database.

Results

Our overall study population is comprised of 13,827 people diagnosed with stage IIIB or IV NSCLC. Of those, 1485 (11%) are classified as having pre-cancer depression, 709 (5%) as having diagnosis-time depression, 1189 (9%) as having post-diagnosis depression and 10,444 (75%) as not having depression. Among 12,851 decedents, we classified 1378 (11%) of subjects with pre-cancer depression, 681 (5%) with diagnosis-time depression, 1055 (8%) with post-diagnosis depression, and 9737 (76%) as without depression. In both the overall study population and among decedents, subjects with pre-cancer depression or diagnosis-time depression are more likely to be female, unmarried, white, Medicaid-eligible, and have a higher co-morbidity score (Tables 1 and 2).

Hospice Use

A majority of subjects, ranging from 58% to 66% across depression categories, utilized hospice after their cancer diagnosis (Table 3). Pre-cancer depression was significantly associated with 90+ days of hospice (adjusted odds ratio [aOR] 1.29, 95% confidence interval [CI] 1.06−1.58) but diagnosis-time or post-diagnosis depression were not associated with lengthy hospice stays. There was no significant association between any category of depression and very short hospice stays (<3 days). Accounting for the competing risk of death, subjects with pre-cancer depression had a 19% higher instantaneous hazard of hospice enrollment (sub-hazard ratio 1.19, 95% CI 1.11−1.28) as did those with diagnosis-time depression (SHR 1.16, 95% CI 1.05−1.29); those with post-diagnosis depression had significantly lower hospice enrollment (SHR 0.80, 95% CI 0.74−0.85).

Hospital Admissions, Emergency Room Visits & Chemotherapy

Multiple inpatient admissions were similar across groups, ranging from 11% to 15% across categories (Table 4). We found slightly lower odds of >1 inpatient admission for patients with pre-cancer depression (aOR 0.74, 95% CI 0.62−0.89) but no association for those with diagnosis-time depression

Table 1

Demographics of 13,827 Subjects With Stage IIIB or IV Non–Small-Cell Lung Cancer, Categorized by Precancer Depression (Three to 24 Months Before Cancer Diagnosis), Diagnosis-Time Depression (Three Months Before to 30 Days After Cancer Diagnosis), Postdiagnosis Depression (31+ Days After Cancer Diagnosis), or No Depression Diagnosis at Any Time

Baseline Characteristics	Precancer Depression, $n = 1485$ (11%)	Diagnosis-Time Depression, $n = 709$ (5%)	Postdiagnosis Depression, $n = 1189$ (9%)	No Depression at Any Time, $n = 10{,}444$ (75%)
Age in yrs (mean ± SD)	77.44 ± 6.87	77.82 ± 6.62	76.01 ± 6.00	77.45 ± 6.64
Gender (*n*, %)				
Female	970 (65%)	414 (58%)	640 (54%)	4800 (46%)
Marital status (*n*, %)				
Married	557 (38%)	310 (44%)	614 (52%)	5308 (51%)
Race (*n*, %)				
White	1342 (90%)	648 (91%)	1036 (87%)	8899 (85%)
Hispanic ethnicity (*n*, %)	70 (5%)	32 (5%)	36 (3%)	450 (4%)
Comorbidity index (mean ± SD)	0.42 ± 0.48	0.31 ± 0.42	0.24 ± 0.35	0.26 ± 0.38
Medicaid eligible (*n*, %)	205 (14%)	89 (13%)	102 (9%)	944 (9%)
Stage (*n*, %)				
IIIB	446 (30%)	199 (28%)	364 (31%)	2713 (26%)
IV	1039 (70%)	510 (72%)	825 (69%)	7731 (74%)
Residence (*n*, %)				
Metropolitan/urban	1311 (88%)	622 (88%)	1060 (89%)	9294 (89%)
SEER registry[a] (*n*, %)				
Northeast	262 (18%)	170 (24%)	299 (25%)	2024 (19%)
Midwest	219 (15%)	106 (15%)	155 (13%)	1355 (13%)
Southeast	451 (30%)	186 (26%)	289 (24%)	2800 (27%)
West	553 (37%)	247 (35%)	446 (38%)	4265 (41%)

[a]SEER registries are categorized as follows: Northeast = Connecticut, New Jersey; Midwest = Detroit, Iowa; Southeast = Atlanta, Kentucky, Louisiana, greater and rural Georgia; West = greater California, Hawaii, Los Angeles, New Mexico, San Francisco, San Jose-Monterey, Seattle, Utah.

(aOR 1.04, 95% CI 0.83–1.30) or for those with postdiagnosis depression (aOR 1.10, 95% CI 0.92–1.32). For reader reference, regression results are listed in Table 5.

ICU admissions were similar across groups, ranging from 21% to 25% (Table 4). We noted lower odds of ICU admission among those with pre-cancer depression (aOR 0.78, 95% CI 0.67–0.90), no association

Table 2

Demographics of 12,851 Deceased Subjects With Stage IIIB or IV Non–Small-Cell Lung Cancer, Categorized by Precancer Depression (Three to 24 Months Before Cancer Diagnosis), Diagnosis-Time Depression (Three Months Before to 30 Days After Cancer Diagnosis), Postdiagnosis Depression (31+ Days After Cancer Diagnosis), or No Depression Diagnosis at Any Time

Baseline Characteristics	Precancer Depression, $n = 1378$ (11%)	Diagnosis-Time Depression, $n = 681$ (5%)	Postdiagnosis Depression, $n = 1055$ (8%)	No Depression at Any Time, $N = 9737$ (76%)
Age in yrs (mean ± SD)	77.62 ± 6.92	77.84 ± 6.63	76.13 ± 6.03	77.62 ± 6.67
Gender (*n*, %)				
Female	887 (64%)	390 (57%)	547 (52%)	4427 (45%)
Marital status (*n*, %)				
Married	508 (37%)	293 (43%)	537 (51%)	4899 (50%)
Race (*n*, %)				
White	1246 (90%)	620 (91%)	921 (87%)	8314 (85%)
Hispanic ethnicity (*n*, %)	66 (5%)	32 (5%)	33 (3%)	425 (4%)
Comorbidity index (mean ± SD)	0.42 ± 0.48	0.31 ± 0.42	0.24 ± 0.36	0.27 ± 0.38
Medicaid eligible (*n*, %)	193 (14%)	86 (13%)	85 (8%)	892 (9%)
Stage (*n*, %)				
IIIB	403 (29%)	185 (27%)	298 (28%)	2387 (25%)
IV	975 (71%)	496 (73%)	757 (72%)	7350 (75%)
Residence (*n*, %)				
Metropolitan/urban	1213 (88%)	597 (88%)	940 (89%)	8653 (89%)
SEER registry[a] (*n*, %)				
Northeast	242 (18%)	166 (24%)	271 (26%)	1892 (19%)
Midwest	202 (15%)	102 (15%)	140 (13%)	1270 (13%)
Southeast	430 (31%)	178 (26%)	255 (24%)	2626 (27%)
West	502 (36%)	235 (35%)	389 (37%)	3949 (41%)

[a]SEER registries are categorized as follows: Northeast = Connecticut, New Jersey; Midwest = Detroit, Iowa; Southeast = Atlanta, Kentucky, Louisiana, greater and rural Georgia; West = greater California, Hawaii, Los Angeles, New Mexico, San Francisco, San Jose-Monterey, Seattle, Utah.

Table 3

Days of Hospice Enrollment Among 13,827 Subjects With Stage IIIB or IV Non–Small-Cell Lung Cancer, Categorized by Precancer Depression (Three to 24 Months Before Cancer Diagnosis), Diagnosis-Time Depression (Three Months Before to 30 Days After Cancer Diagnosis), Postdiagnosis Depression (31+ days After Cancer Diagnosis), or No Depression Diagnosis at Any Time

N, %	Precancer Depression ($n = 1485$)	Diagnosis-Time Depression ($n = 709$)	Postdiagnosis Depression ($n = 1189$)	No Depression History ($n = 10,444$)
Did not enroll	506 (34%)	259 (37%)	499 (42%)	4212 (40%)
Three days or less	133 (9%)	74 (10%)	121 (10%)	1054 (10%)
Four to seven days	166 (11%)	81 (11%)	133 (11%)	1113 (11%)
Eight to 29 days	329 (22%)	150 (21%)	221 (19%)	2156 (21%)
30–89 days	217 (15%)	96 (14%)	128 (11%)	1276 (12%)
90 days or more	134 (9%)	49 (7%)	87 (7%)	633 (6%)

between ICU admission and diagnosis-time depression (aOR 0.90, 95% CI 0.75–1.09), and higher odds of ICU admission and post-diagnosis depression (aOR 1.18, 95% CI 1.01–1.37). Among those with pre-cancer depression, 16% had an in-hospital death compared to 20%–23% of other groups (Table 4). While we noted lower odds of in-hospital death (aOR 0.75, 95% CI 0.64–0.87) among those with pre-cancer depression, we found no association between diagnosis-time depression (aOR 0.86, 95% CI 0.70–1.04) or post-diagnosis depression (aOR 1.16, 95% CI 0.99–1.36) and in-hospital death.

In the last month of life, 7%–9% of subjects had >1 ED visit (Table 4). Pre-cancer depression was associated with lower odds of >1 ED visit in the last 30 days of life (aOR 0.78, 95% CI 0.62–0.98). We observed no association between diagnosis-time depression (aOR 1.04, 95% CI 0.78–1.38) or post-diagnosis depression (aOR 1.15, 95% CI 0.92–1.45) and >1 ED visit. Chemotherapy use in the last 14 days of life was similar across groups, at 11%–12%. We found no significant association between pre-cancer depression (aOR 0.89, 95% CI 0.74–1.07), diagnosis-time depression (aOR 0.98, 95% CI 0.78–1.25) or post-diagnosis depression (aOR 1.07, 95% CI 0.87–1.31) and chemotherapy receipt.

Sensitivity Analyses

In our first set of sensitivity analyses, we fit multivariable logistic regression models after excluding 9% of each group of pre-cancer depression, diagnosis-time depression, and non-depressed subjects (130, 86, and 931 people, respectively) who did not survive at least 30 days following diagnosis. By definition, subjects with post-diagnosis depression had to survive 30 days for categorization, thus were not included in this analysis. Most observed associations between pre-cancer depression, diagnosis-time depression and odds of inpatient admissions, ICU admission, in-hospital death, and chemotherapy use remained unchanged, but the association between pre-cancer depression and >1 ED visits was no longer significant (aOR 0.83, 95% CI 0.65–1.05).

Among 1378 decedents with pre-cancer depression, 894 (65%) were categorized as smokers, whereas 5936 (61%) of 9737 decedents without depression were categorized as smokers. A majority of decedents with diagnosis-time depression (424 of 681, 62%) or post-diagnosis depression (783 of 1,055, 74%) were also categorized as smokers. Our findings between depression and all outcomes were unchanged after including this covariate in our regression models.

Discussion

In an effort to understand how depression may affect healthcare intensity at end of life, we evaluated the association between depression measured at various times before, during, and after a cancer diagnosis on the intensity of end-of-life cancer care

Table 4

End-of-Life Utilization Among 12,851 Decedents With Stage IIIB or IV Non–Small-Cell Lung Cancer, Categorized by Precancer Depression (Three to 24 Months Before Cancer Diagnosis), Diagnosis-Time Depression (Three Months Before to 30 Days After Cancer Diagnosis), Postdiagnosis Depression (31+ Days After Cancer Diagnosis) or No Depression Diagnosis at Any Time

N, %	Pre-cancer Depression ($n = 1378$)	Diagnosis-time Depression ($n = 681$)	Post-diagnosis Depression ($n = 1055$)	No Depression ($n = 9737$)
>1 inpatient admissions	158 (11%)	97 (14%)	160 (15%)	1320 (14%)
ICU admission	291 (21%)	154 (23%)	266 (25%)	2317 (24%)
In-hospital death	224 (16%)	133 (20%)	227 (22%)	2191 (23%)
>1 ED visits	96 (7%)	57 (8%)	100 (9%)	733 (8%)
Chemotherapy in last 14 days	150 (11%)	84 (12%)	123 (12%)	1189 (12%)

ICU = intensive care unit; ED = emergency department.

Table 5

Results of Multivariable Logistic Regression for End-Of-life Utilization Outcomes Among 12,851 Decedents With Stage IIIB or IV Non-small Cell Lung Cancer, Categorized by Pre-cancer Depression (3−24 Months Before Cancer diagnosis), Diagnosis-time Depression (3 Months Before to 30 Days After Cancer diagnosis), Post-diagnosis Depression (31 + days After Cancer diagnosis) Compared to subjects With No Depression diagnosis at any Time

	Pre-cancer Depression	Diagnosis-time Depression	Post-diagnosis Depression
Odds of	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
>1 inpatient admissions	0.74 (0.62−0.89)	1.04 (0.83−1.30)	1.10 (0.92−1.32)
ICU admission	0.78 (0.67−0.90)	0.90 (0.75−1.09)	1.18 (1.01−1.37)
In-hospital death	0.75 (0.64−0.87)	0.86 (0.70−1.04)	1.16 (0.99−1.36)
>1 ED visits	0.78 (0.62−0.98)	1.04 (0.78−1.38)	1.15 (0.92−1.45)
Chemotherapy in last 14 days	0.89 (0.74−1.07)	0.98 (0.78−1.25)	1.07 (0.87−1.31)

aOR = adjusted odds ratio; CI = confidence interval; ICU = intensive care unit; ED = emergency department.

delivery among older adults with advanced NSCLC. Patients with pre-cancer and diagnosis-time depression had higher enrollment in hospice, and those with pre-cancer depression had significantly longer hospice stays. Pre-cancer depression is associated with lower odds of >1 hospitalization, ICU admission, in-hospital death, and multiple ED visits in the last 30 days of life but is not associated with chemotherapy use. Diagnosis-time depression was significantly associated with increased hospice enrollment while post-diagnosis depression was associated with higher odds of ICU admission and lower odds of hospice enrollment.

Our findings that pre-cancer depression is associated with lower-intensity EOL care have potential implications for practice. Specifically, further investigation into the reasons why those with pre-cancer depression receive lower-intensity care may help identify barriers to higher quality care, and inform ways to improve EOL care for cancer patients. It is possible that patients with pre-cancer and diagnosis-time depression were more likely to enroll in hospice as the result of referral patterns to hospice or palliative care services given the presence of depression and other comorbidities, especially given our finding that those with pre-cancer depression had significantly higher odds of 90 + hospice days. Subjects with pre-cancer and diagnosis-time depression had higher comorbidity scores, reflecting more illness. In previous studies, depression or distress was the second-most frequent reason for hospice referral among cancer patients, after uncontrolled pain.[51] As high symptom burden is associated with anxiety and/or depression in advanced cancer patients,[52] those in our pre-cancer depression cohort may have received expedited referrals to palliative or hospice care. Such contact may in turn facilitate hospice entry, as physician factors and EOL care discussions are a significant factor predicting hospice enrollment.[53,54]

Similar to other studies,[44,55] most subjects utilized at least one form of high-intensity EOL care. Subjects with pre-cancer depression had lower odds of >1 inpatient admissions, ICU admission, >1 ED visits, and in-hospital death. Those with diagnosis-time depression had no association with any high-intensity outcomes, but those with post-diagnosis depression had higher odds of ICU admission. Our findings regarding pre-cancer depression are similar to those of Doan and colleagues,[56] who evaluated pre-cancer and post-cancer depression across multiple cancer types and stages at diagnosis in SEER-Medicare. Our findings regarding post-diagnosis depression differ, in that we note an association with higher utilization of ICU admission and lower hospice enrollment. A previous study found an inverse relationship between interventions, ICU use and hospice enrollment among metastatic NSCLC patients,[57] similar to our findings. Overall, our mixed findings recall those of a randomized trial of early palliative care in lung cancer, where depression and anxiety at baseline were associated with intravenous chemotherapy use at EOL but not hospitalization or emergency room use.[58]

We categorized 11% of older adults as having pre-cancer depression, a percentage similar to other studies using SEER-Medicare. Those studies reported percentages of pre-cancer depression ranging from 5% in prostate cancer patients[59] to 7.5% in breast cancer patients[60] and 7.9% in patients with pancreatic cancer.[61] While our claims-based analysis aligns with previous studies, our estimate is likely an under-estimate of depression in this population, as other studies have found depression prevalence ranging from 14%[62] to 28%[7] to 42%[5] among older adults with cancer. In our study population, those with pre-cancer depression were more likely to be female, Medicaid-eligible, white, and not married, similar to the demographics of depressed patients in a prospective observational study of lung cancer patients.[3]

There are multiple limitations to this study. We used a retrospective cohort of decedents for high-intensity outcomes, comprised of sicker patients compared to those who lived beyond the end of the study

observation period. While this introduces selection bias, a previous study has noted that prospective and retrospective analyses of EOL outcomes can produce similar results.[63] Patient/family preferences and social support are determinants of the intensity of EOL care,[64] but as this is a claims-based analysis, we did not have access to information regarding preferences for care, availability of caregiver support, or advance care planning. We did not have access to the results of any screening depression tests (e.g. the Geriatric Depression Scale) or patient response to antidepressant therapy to help confirm our classification of subjects as depressed or not depressed. Subjects may be misclassified if a depressive episode occurred before the two-year look back period of this study. While performance status is associated with depression[4] and higher mortality,[65,66] these data are not available in SEER-Medicare.

Though previous studies have used SEER-Medicare data to explore EOL care among older adults with NSCLC,[56,67-69] this study contributes information regarding the timing of a depression diagnosis, specifically pre-cancer depression, diagnosis-time depression and post-diagnosis depression, and association on healthcare utilization in the last month of life. For oncology and palliative care clinicians, screening for and treating depression following a cancer diagnosis can help assure that patient decision-making capacity is optimal to express their wishes and thus receive goal-concordant EOL care. Our finding that pre-cancer depression is associated with higher enrollment and longer stays in hospice care indicates that hospice organizations may need to additional support to meet the mental health needs of their older enrollees with advanced NSCLC. Finally, future research to elucidate the underlying mechanisms for our observed association between pre-cancer depression and lower-intensity EOL care may help inform ways to facilitate high-quality EOL care for all cancer patients, regardless of depression diagnosis.

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References

1. Bluethmann SM, Mariotto AB, Rowland JH. Anticipating the "Silver Tsunami": prevalence trajectories and comorbidity burden among older cancer survivors in the United States. Cancer Epidemiol Biomarkers Prev 2016;25:1029−1036.

2. McGee SF, Zhang T, Jonker H, et al. The impact of baseline Edmonton Symptom Assessment Scale scores on treatment and survival in patients with advanced non-small-cell lung cancer. Clin Lung Cancer 2018;19:e91−e99.

3. Sullivan DR, Forsberg CW, Ganzini L, et al. Depression symptom trends and health domains among lung cancer patients in the CanCORS study. Lung Cancer 2016;100:102−109.

4. Hopwood P, Stephens RJ. Depression in patients with lung cancer: prevalence and risk factors derived from quality-of-life data. J Clin Oncol 2000;18:893−903.

5. Polanski J, Chabowski M, Chudiak A, et al. Intensity of anxiety and depression in patients with lung cancer in relation to quality of life. Adv Exp Med Biol 2018;1023:29−36.

6. Pirl WF, Traeger L, Greer JA, et al. Depression, survival, and epidermal growth factor receptor genotypes in patients with metastatic non-small cell lung cancer. Palliat Support Care 2013;11:223−229.

7. Nipp RD, El-Jawahri A, Moran SM, et al. The relationship between physical and psychological symptoms and health care utilization in hospitalized patients with advanced cancer. Cancer 2017;123:4720−4727.

8. Fujisawa D, Temel JS, Traeger L, et al. Psychological factors at early stage of treatment as predictors of receiving chemotherapy at the end of life. Psychooncology 2015;24:1731−1737.

9. Singer AE, Meeker D, Teno JM, et al. Factors associated with family reports of pain, dyspnea, and depression in the last year of life. J Palliat Med 2016;19:1066−1073.

10. Prigerson HG, Bao Y, Shah MA, et al. Chemotherapy use, performance status, and quality of life at the end of life. JAMA Oncol 2015;1:778−784.

11. Wright AA, Keating NL, Ayanian JZ, et al. Family perspectives on aggressive cancer care near the end of life. JAMA 2016;315:284−292.

12. Saito AM, Landrum MB, Neville BA, Ayanian JZ, Earle CC. The effect on survival of continuing chemotherapy to near death. BMC Palliat Care 2011;10:14.

13. Bonomi MR, Smith CB, Mhango G, Wisnivesky JP. Outcomes of elderly patients with stage IIIB-IV non-small cell lung cancer admitted to the intensive care unit. Lung Cancer 2012;77:600−604.

14. Natsume M, Watanabe K, Matsumoto S, et al. Factors influencing cancer patients' choice of end-of-life care place. J Palliat Med 2018;21:751−765.

15. Higginson IJ, Daveson BA, Morrison RS, et al. Social and clinical determinants of preferences and their achievement at the end of life: prospective cohort study of older adults

receiving palliative care in three countries. BMC Geriatr 2017;17:271.

16. Planning the Transition to End-of-Life Care in Advanced Cancer (PDQ(R)): Health Professional Version. Bethesda (MD): PDQ Cancer Information Summaries, 2002.

17. Bruera E, Neumann C, Brenneis C, Quan H. Frequency of symptom distress and poor prognostic indicators in palliative cancer patients admitted to a tertiary palliative care unit, hospices, and acute care hospitals. J Palliat Care 2000;16:16–21.

18. Spencer R, Nilsson M, Wright A, Pirl W, Prigerson H. Anxiety disorders in advanced cancer patients: correlates and predictors of end-of-life outcomes. Cancer 2010;116: 1810–1819.

19. Bosworth HB, Hays JC, George LK, Steffens DC. Psychosocial and clinical predictors of unipolar depression outcome in older adults. Int J Ger Psych 2002;7:238–246.

20. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. Med Care 2002;40(8 Suppl):3–18.

21. Ettinger DS, Wood DE, Aisner DL, et al. Non-small cell lung cancer, version 2.2012, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2012;10: 1236–1271.

22. Wang S, Wong ML, Hamilton N, et al. Impact of age and comorbidity on non-small-cell lung cancer treatment in older veterans. J Clin Oncol 2012;30:1447–1455.

23. Bradley CJ, Yabroff KR, Mariotto AB, Zeruto C, Tran Q, Warren JL. Antineoplastic treatment of advanced-stage nonsmall cell lung cancer: treatment, survival and spending (2000 to 2011). J Clin Oncol 2017;35:529–535.

24. Earle CC, Neville BA, Landrum MB, et al. Evaluating claims-based indicators of the intensity of end-of-life cancer care. Int J Qual Health Care 2005;17:505–509.

25. Earle CC, Landrum MB, Souza JM, et al. Aggressiveness of cancer care near the end of life: is it a quality-of-care issue? J Clin Oncol 2008;26:3860–3866.

26. Earle CC, Park ER, Lai B, et al. Identifying potential indicators of the quality of end-of-life cancer care from administrative data. J Clin Oncol 2003;21:1133–1138.

27. Schockett ER, Teno JM, Miller SC, Stuart B. Late referral to hospice and bereaved family member perception of quality of end-of-life care. J Pain Symptom Mange 2005;30: 400–407.

28. Rickerson E, Harrold J, Kapo J, Carroll JT, Casarett D. Timing of hospice referral and families' perceptions of services: are earlier hospice referrals better? J Am Geriatr Soc 2005:819–823.

29. Hwang S, Jayadevappa R, Zee J, et al. Concordance between clinical diagnosis and Medicare claims of depression among older primary care patients. Am J Geriatr Psychiatry 2015;23:726–734.

30. Brocken P, van der Heijden EH, Oud KT, et al. Distress in suspected lung cancer patients following rapid and standard diagnostic programs: a prospective observational study. Psychooncology 2015;24:433–441.

31. Walter FM, Rubin G, Bankhead C, et al. Symptoms and other factors associated with time to diagnosis and stage of lung cancer: a prospective cohort study. Br J Cancer 2015; 112(Suppl 1):S6–S13.

32. Biswas M, Ades AE, Hamilton W. Symptom lead times in lung and colorectal cancers: what are the benefits of symptom-based approaches to early diagnosis? Br J Cancer 2015;112:271–277.

33. Nadpara P, Madhavan SS, Tworek C. Guideline-concordant timely lung cancer care and prognosis among elderly patients in the United States: a population-based study. Cancer Epidemiol 2015;39:1136–1144.

34. Pirl WF, Greer JA, Traeger L, et al. Depression and survival in metastatic non-small-cell lung cancer: effects of early palliative care. J Clin Oncol 2012;30:1310–1315.

35. Mausbach BT, Irwin SA. Depression and healthcare service utilization in patients with cancer. Psychooncology 2017; 26:1133–1139.

36. Nayar P, Qiu F, Watanabe-Galloway S, et al. Disparities in end of life care for elderly lung cancer patients. J Community Health 2014;39:1012–1019.

37. Hardy D, Chan W, Liu CC, et al. Racial disparities in length of stay in hospice care by tumor stage in a large elderly cohort with non-small cell lung cancer. Palliat Med 2012;26:61–71.

38. Shugarman LR, Bird CE, Schuster CR, Lynn J. Age and gender differences in medicare expenditures and service utilization at the end of life for lung cancer decedents. Womens Health Issues 2008;18:199–209.

39. Hardy D, Chan W, Liu CC, et al. Racial disparities in the use of hospice services according to geographic residence and socioeconomic status in an elderly cohort with nonsmall cell lung cancer. Cancer 2011;117:1506–1515.

40. Ornstein KA, Aldridge MD, Mair CA, et al. Spousal characteristics and older adults' hospice use: understanding disparities in end-of-life care. J Palliat Med 2016;19:509–515.

41. Nipp RD, El-Jawahri A, Fishbein JN, et al. The relationship between coping strategies, quality of life, and mood in patients with incurable cancer. Cancer 2016;122: 2110–2116.

42. Iglay K, Santorelli ML, Hirschfield KM, et al. Diagnosis and treatment delays among elderly breast cancer patients with pre-existing mental illness. Breast Cancer Res Treat 2017;166:267–275.

43. Wang SY, Hall J, Pollack CE, et al. Associations between end-of-life cancer care patterns and medicare expenditures. J Natl Compr Canc Netw 2016;14:1001–1008.

44. Wang SY, Hall J, Pollack CE, et al. Trends in end-of-life cancer care in the Medicare program. J Geriatr Oncol 2016;7:116–125.

45. Klabunde CN, Potosky AL, Legler JM, Warren JL. Development of a comorbidity index using physician claims data. J Clin Epidemiol 2000;53:1258–1267.

46. Klabunde CN, Legler JM, Warren JL, Baldwin LM, Schrag D. A refined comorbidity measurement algorithm for claims-based studies of breast, prostate, colorectal, and lung cancer patients. Ann Epidemiol 2007;17:584–590.

47. Zhang X, Zhang MJ, Fine J. A proportional hazards regression model for the subdistribution with right-censored and left-truncated competing risks data. Stat Med 2011;30:1933–1951.

48. Fine JPGR. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;466:496–509.

49. Desai RJ, Solomon DH, Shadick N, Iannaccone C, Kim SC. Identification of smoking using Medicare data–a validation study of claims-based algorithms. Pharmacoepidemiol Drug Saf 2016;25:472–475.

50. Japuntich SJ, Kumar P, Pendergast J, et al. Smoking status and survival among a national cohort of lung and colorectal cancer patients. Nicotine Tob Res 2018 Jan 17. https://doi.org/10.1093/ntr/nty012. [Epub ahead of print].

51. Sasahara T, Watakabe A, Aruga E, et al. Assessment of reasons for referral and activities of hospital palliative care teams using a standard format: a multicenter 1000 case description. J Pain Symptom Manage 2014;47:579–587.e6.

52. Delgado-Guay M, Parsons HA, Li Z, Palmer JL, Bruera E. Symptom distress in advanced cancer patients with anxiety and depression in the palliative care setting. Support Care Cancer 2009;17:573–579.

53. Obermeyer Z, Powers BW, Makar M, Keating NL, Cutler DM. Physician characteristics strongly predict patient enrollment in hospice. Health Aff (millwood) 2015;34:993–1000.

54. Mack JW, Weeks JC, Wright AA, Block SD, Prigerson HG. End-of-life discussions, goal attainment, and distress at the end of life: predictors and outcomes of receipt of care consistent with preferences. J Clin Oncol 2010;28:1203–1208.

55. Earle CC, Neville BA, Landrum MB, et al. Trends in the aggressiveness of cancer care near the end of life. J Clin Oncol 2004;22:315–321.

56. Doan K, Levy B, Gross CP, Wang SY. Associations between pre- and post-cancer depression diagnoses and end-of-life cancer care intensity. J Clin Pathways 2016;2:47–54.

57. Tukey MH, Faricy-Anderson K, Corneau E, Youssef R, Mor V. Procedural aggressiveness in veterans with advanced non-small-cell lung cancer at the end of life. J Palliat Med 2018;21:445–451.

58. Temel JS, McCannon J, Greer JA, et al. Aggressiveness of care in a prospective cohort of patients with advanced NSCLC. Cancer 2008;113:826–833.

59. Prasad SM, Eggener SE, Lipsitz SR, et al. Effect of depression on diagnosis, treatment, and mortality of men with clinically localized prostate cancer. J Clin Oncol 2014;32:2471–2478.

60. Goodwin JS, Zhang DD, Ostir GV. Effect of depression on diagnosis, treatment, and survival of older women with breast cancer. J Am Geriatr Soc 2004;52:106–111.

61. Boyd CA, Benarroch-Gampel J, Sheffield KM, et al. The effect of depression on stage at diagnosis, treatment, and survival in pancreatic adenocarcinoma. Surgery 2012;152:403–413.

62. Pan X, Sambamoorthi U. Health care expenditures associated with depression in adults with cancer. J Community Support Oncol 2015;13:240–247.

63. Setoguchi S, Earle CC, Glynn R, et al. Comparison of prospective and retrospective indicators of the quality of end-of-life cancer care. J Clin Oncol 2008;26:5671–5678.

64. Mack JW, Cronin A, Keating NL, et al. Associations between end-of-life discussion characteristics and care received near death: a prospective cohort study. J Clin Oncol 2012;30:4387–4395.

65. Faller H, Schmidt M. Prognostic value of depressive coping and depression in survival of lung cancer patients. Psychooncology 2004;13:359–363.

66. Stommel M, Given BA, Given CW. Depression and functional status as predictors of death among cancer patients. Cancer 2002;94:2719–2727.

67. Cooke CR, Feemster LC, Wiener RS, O'Neil ME, Slatore CG. Aggressiveness of intensive care use among patients with lung cancer in the Surveillance, Epidemiology, and End Results-Medicare registry. Chest 2014;146:916–923.

68. Warren JL, Barbera L, Bremner KE, et al. End-of-life care for lung cancer patients in the United States and Ontario. J Natl Cancer Inst 2011;103:853–862.

69. Guadagnolo BA, Liao KP, Elting L, et al. Use of radiation therapy in the last 30 days of life among a large population-based cohort of elderly patients in the United States. J Clin Oncol 2013;31:80–87.

Appendix

International Classification of Disease, Oncology (ICD-O) histology codes used to define non-small cell lung cancer:

Code	Description
8010/3	Carcinoma
8012/3	Large cell carcinoma
8020/3	Carcinoma, undifferentiated, NOS
8022/3	Pleomorphic carcinoma
8031/3	Giant cell carcinoma
8032/3	Spindle cell carcinoma, NOS
8033/3	Pseudosarcomatous carcinoma
8046/3	Non-small cell carcinoma
8050/3	Papillary carcinoma, NOS
8052/3	Squamous cell papilloma, NOS
8070/3	Squamous cell carcinoma, NOS
8071/3	Squamous cell carcinoma, keratinizing, NOS
8072/3	Squamous cell carcinoma, large cell, nonkeratinizing, NOS
8073/3	Squamous cell carcinoma, small cell, nonkeratinizing
8074/3	Squamous cell carcinoma, spindle cell
8140/3	Adenocarcinoma, NOS
8250/3	Bronchiolo-alveolar adenocarcinoma, NOS
8251/3	Alveolar adenocarcinoma
8252/3	Bronchiolo-alveolar carcinoma, non-mucinous
8253/3	Bronchio-alveolar carcinoma, mucinous
8255/3	Adenocarcinoma with mixed subtypes
8260/3	Papillary adenoma, NOS
8310/3	Clear cell adenocarcinoma, NOS
8323/3	Mixed cell adenocarcinoma
8480/3	Mucinous adenocarcinoma
8481/3	Mucin-producing adenocarcinoma
8490/3	Signet ring cell carcinoma
8550/3	Acinar cell carcinoma
8560/3	Adenosquamous carcinoma
8570/3	Adenocarcinoma with squamous metaplasia

Generic names of systemic agents used for determination of chemotherapy/targeted agent receipt:

Afatinib	Docetaxel	Mitomycin
Albumin-bound paclitaxel	Erlotinib	Paclitaxel
Bevacizumab	Etoposide	Pemetrexed
Carboplatin	Gemcitabine	Trastuzumab
Cetuximab	Gefitinib	Vinorelbine
Cisplatin	Ifosfamide	Vinblastine
Crizotinib	Irinotecan	

We also utilized following Healthcare Common Procedure Coding System (HCPCS) indicating chemotherapy administration or agents: J8999, J9999, V5811, V662, V667.