The Impact of Depression on Patient Outcomes among Older Adults with Lung Cancer

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Abstract

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Background:

Depression is a common malady among older adults, and as the incidence of cancer increases with age, older adults may be living with both cancer and depression. Previous studies have assessed the impact of depression on patient outcomes when depression is measured around the time of a cancer diagnosis or during cancer treatment, but we know very little about how depression preceding the cancer diagnosis affects patient outcomes during the course of cancer treatment. Using the example of lung cancer, the most common cause of cancer death among older adults, we examined the association between pre-existing depression and cancer stage at diagnosis, survival, and health care utilization.

Methods:

We used the national Surveillance, Epidemiology, and End Results (SEER) database, linked to Medicare healthcare and prescription claims, to examine the association between pre-existing depression and patient outcomes for older adults with non-small cell lung cancer (NSCLC) diagnosed between 2008-2011 with claims from 2007-2013. We used multivariate logistic regression models to investigate the association of pre-existing depression, advanced NSCLC stage at diagnosis, and receipt of aggressive end-of-life care. We estimated multivariate Cox proportional hazards models to examine the association

of pre-existing depression and overall survival. We utilized competing risk regression models to examine the relationship between pre-existing depression and time to anticancer therapy or hospice enrollment.

Results:

We included 24,666 people in our analysis. Older adults with pre-existing depression were less likely to be diagnosed with advanced stage NSCLC (OR 0.76, 95% CI 0.68-0.85). Of the 8,873 older adults with stages 1-3A NSCLC, persons with pre-existing depression and stage 1 NSCLC had a higher risk of death compared to those without depression (OR 1.19, 95% CI 1.01-1.41). We found similar patterns of anticancer therapy receipt between older adults with or without pre-existing depression, and no significant difference in time to first anticancer treatment, accounting for the competing risk of death. Among 14,385 decedents with stage 3B or 4 NSCLC, those with pre-existing depression were more likely to enroll in hospice than persons without depression (SHR 1.16, 95% CI 1.06-1.28). We found no difference in utilization of inpatient hospitalizations, emergency room use, or chemotherapy receipt in the last 30 days of life, comparing those with versus those without pre-existing depression.

Discussion:

In a national sample of older adults with NSCLC, pre-existing depression was associated with earlier stage at cancer diagnosis, shorter survival among those with early stage NSCLC and higher hospice utilization among persons with advanced NSCLC. These findings indicate the importance of screening for and treating depression during cancer therapy. As people with pre-existing depression are more likely to enroll in hospice, it is important that hospice organizations and caregivers have sufficient support to address cancer and mental health concerns at end-of-life.

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Chapter One

The impact of pre-existing depression on stage at diagnosis, treatment receipt, and survival among older adults with non-small cell lung cancer

ABSTRACT

Background:

Studies have found that depression present at the time of a cancer diagnosis or during cancer treatment negatively impacts patient outcomes, but little information is available regarding the association between depression prior to the cancer diagnosis and patient outcomes. We evaluated the relationship between pre-existing depression and cancer stage at diagnosis, anticancer therapy receipt, and overall survival in a national sample of older adults with non-small cell lung cancer (NSCLC).

Methods:

We use the SEER-Medicare database, containing records for older adults with NSCLC diagnosed between 2008-2011with claims from 2007-2013. We used a multivariate logistic regression model to assess the outcome of cancer stage at diagnosis, a competing risk regression model to evaluate time to anticancer therapy, and a multivariate Cox proportional hazards model to examine the association of pre-existing depression and overall survival.

Results:

Among 24,666 older adults with stage 1-4 NSCLC, those with pre-existing depression were less likely to be diagnosed with advanced stage NSCLC (OR 0.76, 95% CI 0.68-0.85). Evaluating the 8,873 people with stages 1-3A NSCLC, pre-existing depression was associated with a higher risk of death in a pooled analysis of all stages (HR 1.15, 95% CI 1.01-1.30) among those with stage 1 NSCLC (HR 1.19, 95% CI 1.01-1.41). We found no significant difference in time to first anticancer therapy.

Discussion:

We found that pre-existing depression was associated with earlier stage at cancer diagnosis, but also a higher risk of mortality. Screening cancer patients for a history of depression and treating depression during cancer treatment may help address this survival difference.

Background

Depression accompanying or following a lung cancer diagnosis is associated with deleterious patient outcomes. The presence of depression following a cancer diagnosis is associated with significantly longer hospitalizations [1] and poorer adherence to therapy and attendance at oncology appointments.[2] The presence of post-diagnosis depression results in shorter survival compared to patients without depression. [2-5]The American Society of Clinical Oncology has explicitly acknowledged that depression prior to a cancer diagnosis is a risk factor for poor outcomes and should be considered in patient assessment and care planning. [6]

Limited information is available regarding the impact of depression identified prior to a lung cancer diagnosis on subsequent survival and cancer treatment receipt. One study found an increased incidence of lung cancer among those with pre-existing depression, and lower survival following the cancer diagnosis. [7] A meta-analysis reported higher mortality among subjects with pre-existing depression [8]while another study noted that previous depression or limited functional status resulted in a 2.6 times greater hazard of dying than patients without such health issues. [9] In a study of veterans in the Pacific Northwest, Sullivan and colleagues found increased mortality in subjects with stage I/II non-small cell lung cancer (NSCLC) but no difference in subjects with stage III/IV NSCLC [10] and no significant overall association between receipt of chemotherapy and pre-existing depression. [11]

Other population-based studies using Surveillance, Epidemiology, and End Results (SEER) data linked to Medicare claims data have explored a past diagnosis of depression and the impact on patient outcomes among older adults with other cancers [12-15] finding that pre-existing depression is negatively associated with survival, and in some cases, treatment receipt. To our knowledge, the impact of pre-existing depression on stage at diagnosis, anticancer treatment receipt, and survival has not been ascertained in a nationwide, population-based sample. We used the SEER-Medicare database to evaluate our hypothesis that depression preceding a lung cancer diagnosis is associated with advanced

stage at diagnosis, longer time to anticancer therapy, and lower overall survival among older adults with NSCLC.

Patients and Methods

Study population

We utilized the national SEER-Medicare linked database for our analysis, which contains Medicare claims from 1991 linked to subjects in the National Cancer Institute's SEER dataset. The linkages are updated approximately every four years; the most recent linkage is for cancer diagnoses through 2011 with claims through 2013. The data for 94% of subjects 65 and older in the SEER registries are successfully linked to the Medicare enrollment file, and the age and gender distribution in the database is similar to the population of older adults in the United States. [16]

We included all patients with a NSCLC diagnosis who were continuously enrolled in fee-for-service Medicare parts A and B for at least 12 months prior to diagnosis. To evaluate Part D claims in our analysis, we included subjects with NSCLC diagnoses from 2008-2011; the available claims for this population range from 2007-2013. We excluded patients diagnosed at autopsy or by death certificate, those who were diagnosed with other cancers or enrolled in a Medicare Advantage plan, those without any claims in the year prior to their NSCLC diagnosis, and subjects who qualified for Medicare based on end-stage renal disease or disability rather than age. We also excluded patients with primary occult cancer, unknown cancer stage, missing demographic information, or a diagnosis of bipolar disorder or schizophrenia. Figure 1 includes a diagram of inclusion and exclusion criteria with the resulting sample size. The Institutional Review Board of the Fred Hutchinson Cancer Research Center approved this study.

Definition of depression

We used the following International Classification of Disease, version 9 (ICD-9) codes to define depression claims: 296.2, 296.3, 300.4, 309, 309.1, 311.[12,17,18] We looked for a claim with a depression diagnosis, a claim with the Healthcare Common Procedure Coding System (HCPCS) code G8431or G8511 (positive depression screen, with or without documented treatment plan) or 2 or more prescriptions for antidepressants. [19,20]

We defined two groups for analysis; those with pre-existing depression ("depressed") and those without depression. We classified subjects as having pre-existing depression if their claims history met the aforementioned criteria within a 3 to 12 month window prior to the initial lung cancer diagnosis. As mean symptom lead time to diagnosis is approximately 3 months for lung cancer, [21-24] we excluded patients with a first depression code appearing in the 3 months prior to diagnosis. We used this to exclude depression associated with the diagnostic work-up for lung cancer or the possibility of receiving a diagnosis of lung cancer rather than a pre-existing condition. Depression following a lung cancer diagnosis has been explored previously [25-27] thus we also excluded patients whose first depression codes appeared following the date of lung cancer diagnosis. As anxiety often co-occurs with depression, we classified subjects based on the depression diagnosis, and created a covariate to control for the presence of concomitant anxiety among depressed subjects. We created a comparison group using the same inclusion and exclusion criteria, comprised of subjects without any claims for depression or anxiety at any time during the study period.

Medication use

We selected Part D claims for antidepressant medication use prior to the NSCLC diagnosis. Previous studies have looked at a wide range of medications that may be used in depression, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), serotonin modulators, tricyclic antidepressants, and atypical

antidepressants such as bupropion. [28,29] Since MAOIs and tricyclic antidepressants are not considered to be optimal therapy for depression in older adults, [30] we did not include these in our analysis. We included the following medications: bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, levomilnacipran, milnacipran, mirtazapine, nefazodone, paroxetine, sertraline, venlafaxine, and vilazodone.

Covariates

We grouped SEER registries geographically 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). We used the National Cancer Institute composite (Klabunde-Charlson) comorbidity index [31 32] for comorbidity calculations. Based on previous studies, we identified additional *a priori* confounders that affect health care utilization and patient outcomes in lung cancer and depression, including race, [11,33] Hispanic ethnicity, [34] gender, [33] cancer stage, [10] age, [11] socioeconomic status, [35] marital status [36] and rural residence. [35,37,38]

Statistical Analyses

We computed descriptive statistics for subjects with and without a history of depression, comparing groups on age at diagnosis, sex, marital status, race, Hispanic ethnicity, Klabunde comorbidity index, SEER registry, Medicaid eligibility, urban residence, and lung cancer stage. We used the student's t-test for continuous variables and the chi-square test for categorical variables to assess differences between the depressed and non-depressed subjects.

We conducted a multivariate logistic regression to evaluate the association between pre-existing depression and advanced (3B/4) stage at diagnosis. For time to first anticancer therapy among patients potentially receiving curative therapy (stages 1, 2, 3A), we performed a competing risk

regression based on Fine-Gray [39,40] to account for the competing risk of death prior to treatment receipt. We stratified time to treatment analysis by cancer stage. For survival analysis, we used a Cox proportional hazards model with a time-varying covariate for receipt of anticancer therapy. We adjusted for the aforementioned covariates for both the competing risk and Cox proportional hazard models. All analyses were performed using SAS statistical software, version 9.4 (SAS Institute Inc, Cary, NC) and Stata statistical software, version 14.1 (StataCorp, College Station, TX).

Sensitivity analysis

We evaluated the impact of a more restrictive definition of depression on our study results. In sensitivity analysis, we classified subjects with pre-existing depression if they had 1 inpatient or 2 outpatient claims for depression in the 3 to 12 months preceding their NSCLC diagnosis, or an outpatient claim for depression with an accompanying pharmacy claim for an antidepressant.

Results

Our initial study population included 24,666 older adults with stages 1-4 NSCLC (Table 1a). Sixteen percent (n=3949) of subjects were classified as having pre-existing depression. Depressed subjects were significantly more likely to be female, younger, unmarried, white, Medicaid eligible, diagnosed with stage 1 NSCLC, and have higher Klabunde comorbidity scores.

Pre-existing depression and stage at diagnosis

In multivariate logistic regression (Table 2), pre-existing depression was associated with lower odds of being diagnosed with advanced stage NSCLC (odds ratio (OR) 0.76, 95% confidence interval (CI) 0.68-0.85) after adjustment for age, gender, race, marital status, comorbidity index, Hispanic ethnicity,

rural residence, Medicaid enrollment, SEER registry, concomitant anxiety, and receipt of antidepressants prior to diagnosis.

Receipt of anticancer therapy

We noted the receipt of anticancer therapy, defined as chemotherapy, surgery, and/or radiation (Table 3). Among older adults with stage 1 NSCLC, those with depression received surgery-only less often than those without depression (40% vs 43%) and chemotherapy-only and radiation-only more often (5% vs 3% and 18% vs 15%, respectively). We observed a similar percentage of patients receiving no anticancer therapy among stage 1 patients (13% vs 12%) however a higher percentage of depressed patients did not receive any anticancer therapy compared to those without depression among stage 2 (16% vs 11%) and stage 3A (21% vs 18.5%) patients. Comparing depressed and non-depressed patients with stage 2 NSCLC, treatment receipt was within 1% between groups with the exception of surgery plus radiation and chemotherapy, radiation & surgery, with more non-depressed patients receiving treatment in these categories compared to those with depression (5% vs 2%, and 16% vs 11%). Among patients with stage 3A NSCLC, the percentage difference in treatment received was 1% or less across categories except for chemotherapy & radiation, where 39% of depressed patients received such treatment compared to 41.5% of non-depressed patients, and radiation only, where 13% of depressed patients received that treatment versus 11% of non-depressed individuals. Across all stages of cancer, subjects with pre-existing depression had similar median days to first treatment when compared to subjects without pre-existing depression (Table 4).

Time to anticancer therapy

For our analysis of time to first anticancer therapy, we included subjects with stages 1, 2, or 3A non-small cell lung cancer (Table 1b), which comprised 8,873 subjects from our original population. Of

those, we classified 1649 (17%) as having pre-existing depression. Again, subjects with depression were significantly more likely to be female, younger, white, not married, Medicaid eligible, diagnosed with stage 1 NSCLC, and have higher comorbidity scores.

We found no significant association between pre-existing depression and time to first anticancer therapy (Table 5) among subjects with stage 1 NSCLC (subhazard ratio (SHR) 0.98, 95% CI 0.87-1.11), stage 2 NSCLC (SHR 0.83, 95% CI 0.62-1.12) or stage 3A NSCLC (SHR 0.81, 95% CI 0.66-1.01).

Overall survival

Subjects with pre-existing depression and stage 1 or stage 2 NSCLC had lower median days survived (883 and 510.5 days, respectively) compared to those without pre-existing depression (975 days and 676.5 days, respectively), and subjects with stage 3A NSCLC and pre-existing depression had similar median survival compared to those without pre-existing depression (366 and 362 days, respectively) (Table 6).

After controlling for covariates of interest (Table 7), we noted a higher risk of death across all stages among those with pre-existing depression (hazard ratio (HR) 1.15, 95% CI 1.01-1.30). We observed a higher risk of death in depressed patients with stage 1 NSCLC (HR 1.19, 95% CI 1.01-1.41) however we did not find a statistically significant increased risk of death among subjects with stage 2 NSCLC (HR 1.03, 95% CI 0.92-1.85) or stage 3A NSCLC (HR 1.14, 95% CI 0.92-1.41).

Sensitivity analyses

Using a more restrictive depression definition, we classified 8% of our study population across stages 1-4 as having pre-existing depression while 9% of those with stages 1-3A NSCLC had pre-existing depression. Again, we found that patients with pre-existing depression were less likely to be diagnosed with advanced stage cancer (OR 0.82, 95% CI 0.72-0.93), and found no significant difference in time to

anticancer therapy among patients with stage 1 NSCLC (SHR 0.96, 95% CI 0.83-1.10), stage 2 NSCLC (SHR 1.05, 95% CI 0.77-1.42) or stage 3A NSCLC (SHR 0.98, 95% CI 0.78-1.23). Unlike our primary analysis, we found no significant difference in survival across all stages (HR 1.02, 95% CI 0.90-1.17), or among those with stage 1 (1.07, 95% CI 0.89-1.28), stage2 (HR 1.21, 95% CI 0.83-1.76), or stage 3A NSCLC (HR .96, 95% CI 0.75-1.23).

Discussion

We found that depression occurring prior to the cancer diagnosis has a negative impact on patient survival. Although we also found that people with depression have higher odds of an early stage cancer diagnosis, they also have higher mortality. This finding points to the need to focus additional effort and resources on mental health during cancer treatment.

Similar to other studies, [15,41] our study population with depression was more likely to be female, not married, and white. Our finding that 17% of our study subjects have depression is similar to another claims-based analysis of pre-existing depression in lung cancer which found 14% of patients to have pre-existing depression; [10] a prevalence study of lung cancer patients in the United Kingdom noted that 13% of NSCLC patients were depressed at diagnosis. [42] As many smokers later develop NSCLC, we compared our depression classification to the measurements of depression among smokers. Among smokers calling a California quit line, 24% exhibited symptoms of depression using a validated screening tool, [43] a higher percentage than we have found in this study.

Our finding that patients with pre-existing depression were less likely to be diagnosed with advanced cancer may be explained by the presence of comorbidities and resultant contact with health care providers. The depressed subjects in our study had significantly higher Klabunde comorbidity scores, reflecting a higher burden of illness, compared to subjects without pre-existing depression. In other studies, Ades and colleagues noted that patients with earlier stage lung cancer were more often

diagnosed via X-ray in the primary care setting [44] while Zafar et al found that colorectal cancer patients with higher comorbidity were more likely to be diagnosed with earlier stage cancer [45] and overall comorbid illnesses may predict greater receipt of cancer screening. [46] Thus, increased contact with primary care due to mental health or other concerns related to their comorbidities may have contributed to the lower odds of advanced stage at diagnosis that we observed in this study.

We did not find a statistically significant difference between time to first anticancer therapy receipt between subjects with pre-existing depression and those without, a result which is similar to findings from other studies. Greer et al noted that patients with baseline depression and advanced NSCLC did not experience chemotherapy dose delays or dose reductions compared to their non-depressed counterparts. [47] In a study involving veterans in the Pacific Northwest, Sullivan and colleagues found no significant overall association between receipt of chemotherapy and depression existing prior to the lung cancer diagnosis. [11]

Following adjustment for covariates and treatment receipt, we found a 15% higher risk of death comparing subjects with pre-existing depression to those without depression, similar to the results of other studies. [8,9] Our findings are similar to those in previous research; a randomized controlled trial of early palliative care in metastatic NSCLC, major depression predicted worse survival. [48] Other studies have found increased mortality among patients with pre-existing depression and pancreatic, [15] breast [12] or prostate [14] cancers. Similar to the findings of Sullivan and colleagues [10] we noted decreased survival among patients with stage 1 NSCLC. Of note, the survival difference observed in this study is greater than the survival difference afforded by receipt of conventional therapies.[49]

Limitations

As this study is a retrospective claims analysis, we did not have access to electronic medical records to determine the results of any screening tests in clinic, document patient or provider

preferences for cancer or depression treatment, or patient response to antidepressant therapy. Given that we looked 12 months back from initial diagnosis, it is possible that subjects may be not categorized properly as depressed or non-depressed if an episode of depression occurred beforehand.

We do not have access to functional status in claims, and other studies have found that low performance status is associated with depression [50] and also predicts mortality.[9,51] There is an established association between depression and smoking, [52] both of which may predict negative patient outcomes. Smoking during cancer therapy is also associated with worse outcomes[53] but smoking status is not available in the SEER-Medicare database. One of the potential reasons for the observed survival difference may be the result of smoking status; if depressed subjects have greater consumption of cigarettes, they may have higher mortality.

For the years of this analysis, the percentage of Medicare enrollees who had Part D coverage in the year before their diagnosis increased from 48.8% in 2007 to 53.3% in 2013.[54] As we do not have Part D claims for a portion of our population, this will lead to under-detection of those using antidepressants, because antidepressants are part of our algorithm for identifying people with pre-existing depression. Additionally, as depression among older adults if often underdiagnosed, [55-57] and patients with depression may not have an associated claim for depression in their Medicare claims, we may not be capturing an accurate representation of depression in this population. [58,59]

Conclusion

This study builds upon previous research by using a national, population-based sample of older adults to evaluate the association between pre-existing depression and outcomes in NSCLC. Despite pre-existing depression being associated with higher odds of an earlier cancer diagnosis, which should portend a favorable survival differences, we found an increased risk of mortality among subjects with pre-existing depression. As the survival decrement associated with depression is greater than the

survival gain afforded to patients by chemotherapy receipt, depression amelioration is an important focus for improving overall survival among lung cancer patients. Patients with a history of depression should be identified through screening in oncology clinics and be offered depression treatment to decrease this difference.

Chapter Two

The association between pre-existing depression and end-of-life care among older adults with metastatic non-small cell lung cancer

ABSTRACT

Background:

Lung cancer is often diagnosed at an advanced stage and the intent of cancer treatment for metastatic disease is palliative. Distress following a terminal diagnosis is common, and studies have evaluated the association between end-of-life (EOL) care and psychological distress measured at or after a cancer diagnosis. However, the connection between pre-existing depression and EOL care for older adults with NSCLC has not been explored. We assessed the relationship between pre-existing depression and use of hospice, hospital admissions, emergency department visits, and chemotherapy receipt at EOL.

Methods:

We used the national SEER-Medicare database for this study. We utilized multivariate logistic regression models to explore the association of pre-existing depression with receipt of aggressive end-of-life care, defined as emergency department visits, chemotherapy receipt, and hospital admissions in the last 30 days of life. We created competing risk regression models to study the relationship between pre-existing depression and time to hospice enrollment.

Results:

Of the 14,385 decedents with stage 3B or 4 NSCLC, older adults with pre-existing depression had a higher likelihood of hospice enrollment than people without depression (SHR 1.16, 95% CI 1.06-1.28). Pre-existing depression was associated with significantly decreased odds of terminal hospital admissions (OR 0.76, 95% CI 0.63-0.92). We found no significant difference in the odds of inpatient hospitalizations (OR 1.05, 95% CI 0.89-1.22), intensive care unit admissions (OR 0.85, 95% CI 0.70-1.03), emergency room use (OR 0.93, 95% CI 0.79-1.08), or chemotherapy receipt (OR 0.92, 95% CI 0.75-1.13) in the last 30 days of life.

Discussion:

Older adults with pre-existing depression were significantly more likely to enroll in hospice compared to those without depression. Hospice organizations may benefit from increased resources to address mental health needs at EOL. Approximately half of all study subjects utilized at least one form of aggressive EOL care. Augmented support to caregivers and patients at EOL may reduce such utilization.

Background

People with depression are more likely to be diagnosed with lung cancer compared to those without depression. [4,7]Lung cancer is often diagnosed at an advanced stage, where treatment options focus on symptom palliation and quality of life. We know little about how depression preceding the diagnosis impacts the lung cancer care trajectory, especially at end-of-life (EOL). Most research has focused on depression existing at the time of a lung cancer diagnosis or following the cancer diagnosis, as distress commonly accompanies such a diagnosis and the incidence of depression increases as death nears. [60] One study found that depression measured around the time of diagnosis was associated with higher likelihood of using intravenous chemotherapy at EOL.[61]

Studies have suggested that while many patients and family members prefer less intensive care at EOL, this is often not provided.[62] Aggressive EOL care, defined as intensive care unit admission, hospitalization or emergency room visits in the last 30 days of life, chemotherapy use in the last 14 days of life, and less than 3 days of hospice use or no hospice use, [63-65] is associated with poorer patient quality of life, [66] does not confer a survival benefit, [67,68]and may conflict with patient or family preferences. [69,70] Psychological distress has been found to negatively impact hospice enrollment.[71]

While other population-based studies have used Surveillance, Epidemiology, and End Results (SEER) data linked to Medicare claims data to explore EOL care among older adults with NSCLC, [72-74] none have evaluated the relationship between pre-existing depression and EOL care among this cohort. Herein, we used the SEER-Medicare database to evaluate our hypothesis that depression preceding a lung cancer diagnosis is associated with greater use of aggressive EOL care and lower use of hospice.

Patients and Methods

Study population

For this analysis, we used the SEER-Medicare database, comprised of Medicare claims from 1991 linked to clinical data for subjects in the National Cancer Institute's SEER dataset. The clinical records of 94% of subjects 65 and older in the SEER registries are connected to Medicare claims, and the demographic distribution in the database reflects the population of older adults in the United States. [16]

We included subjects with NSCLC diagnoses from 2008-2011, who have claims, including Part D prescription drug claims, from 2007-2013. We required that all subjects had continuous enrollment in fee-for-service Medicare parts A and B for at least 12 months prior to diagnosis to calculate a comorbidity score and evaluate for pre-existing 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 in the year prior to their NSCLC diagnosis, and people who qualified for Medicare based on end-stage renal disease. We eliminated records for subjects with missing demographic information or a diagnosis of bipolar disorder or schizophrenia. As this study focused on EOL care, we excluded subjects who did not die during the study period. Our study criteria and resulting population appear in Figure 1. The Institutional Review Board of the Fred Hutchinson Cancer Research Center approved this study.

Definition of depression

We defined depression using the following International Classification of Disease, version 9 (ICD-9) codes: 296.2, 296.3, 300.4, 309, 309.1, 311.[12,17,18] We utilized inpatient, outpatient, carrier, and Part D claims files to look for a claim for depression or 2 or more prescriptions for an antidepressant, [19,20] or a claim with the Healthcare Common Procedure Coding System (HCPCS) codes G8431or G8511 (positive depression screen, with or without documented treatment plan).

If subjects had claims meeting the aforementioned depression criteria in the 3 to 12 months preceding their NSCLC diagnosis, then we classified the subject as having pre-existing depression. We

excluded patients with a first depression code appearing in the 3 months preceding diagnosis, [21-24] given that this is the most typical timeframe between symptom lead time and the lung cancer diagnosis, and depression during this time may be depression associated with the diagnostic work-up for lung cancer or the possibility of receiving a diagnosis of lung cancer rather than a pre-existing condition.

As depression assessed after diagnosis has been explored, [48,75] we also excluded patients whose first depression codes appeared following the date of lung cancer diagnosis. Finally, as many people with depression also experience anxiety, [76] which may also affect EOL decision making, [77] we controlled for co-occurring anxiety among depressed subjects. Subjects without any claims for depression or anxiety at any time during the study period comprised the comparison group.

Medication use

We used Part D claims to ascertain antidepressant use prior to diagnosis. We included selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), serotonin modulators, and atypical antidepressants, specifically: bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, levomilnacipran, milnacipran, mirtazapine, nefazodone, paroxetine, sertraline, venlafaxine, and vilazodone. [28,29] We excluded monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants from our analysis as they are not favored treatment options in older adults. [30]

Covariates

We identified confounders *a priori*, focusing on those affecting health care utilization and EOL outcomes in lung cancer and depression, including race, [78] Hispanic ethnicity, [79] gender, [80] age [80] socioeconomic status, [81] marital status, [82] and rural residence. [78] To control for possible geographic differences, 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. [31,32]

Statistical Analyses

We calculated descriptive statistics to compare subjects with and without a history of depression, controlling for age at diagnosis, sex, marital status, race, Hispanic ethnicity, Klabunde comorbidity index, SEER registry, Medicaid eligibility, urban residence, and lung cancer stage. We used the student's t-test for continuous variables and the chi-square test for categorical variables.

We constructed multivariate logistic regression models to evaluate the association between pre-existing depression and the odds of emergency room visits, inpatient hospitalization, terminal admission, intensive care unit (ICU) admission, and chemotherapy receipt in the last 30 days of life. Because patients with advanced cancer may die before they have a chance to enroll in hospice, we modeled a competing risk regression for time to hospice enrollment, with the competing risk of death. [39,40] We adjusted for the aforementioned covariates in all regression and risk models and performed all analyses using SAS statistical software, version 9.4 (SAS Institute Inc, Cary, NC) and Stata statistical software, version 14.1 (StataCorp, College Station, TX).

Sensitivity analysis

We conducted a sensitivity analysis using a more restricted definition of depression to evaluate the effect on our findings. We utilized the same ICD-9 codes as in our primary analysis, but required that subjects have 1 inpatient claim, 2 or more outpatient claims, or an outpatient claim for depression with an accompanying claim for an antidepressant to be categorized as having pre-existing depression.

Results

Our study population consisted of 14,385 older adults with stages 3B or 4 NSCLC who died during the observation period (Table 8). Depressed subjects (n=2082, 14%) were significantly more likely to be female, unmarried, white, live in rural areas, have higher Klabunde comorbidity scores, and be diagnosed with stage 3B NSCLC rather than stage 4 disease compared to those without a history of depression (n=12303, 86%).

Hospice use

Sixty-nine percent of depressed subjects and 63% of non-depressed subjects utilized hospice after their cancer diagnosis (Table 9). Among subjects with pre-existing depression, 36% enrolled in hospice in the last 7 days of life compared to 37% of those without pre-existing depression. Most subjects received hospice services within 30 days of death—68% of subjects with pre-existing depression compared to 70% of those without. Accounting for the competing risk of death, subjects with pre-existing depression had a 16% higher hospice enrollment than those without depression (sub hazard ratio 1.16, 95% confidence interval (CI) 1.06-1.28) (Table 10).

Hospital admissions, emergency room visits & chemotherapy

Across both groups, 58% had an inpatient admission in the last 30 days of life (Table 11). Intensive care unit (ICU) admissions were similar across groups, as 21% and 24% of depressed and non-depressed subjects, respectively, experienced an ICU admission. Of non-depressed subjects, 27% had a terminal admission, compared to 23% of those with pre-existing depression. We found no statistically significant association between pre-existing depression and inpatient admission (odds ratio (OR) 1.05,

95% CI 0.89-1.22), or ICU admission (OR 0.85, 95% CI 0.70-1.03). We did note lower odds of terminal admission (OR 0.76, 95% CI 0.63-0.92) among those with pre-existing depression (Table 12).

Approximately half of each group had at least 1 emergency department (ED) visit in the last month of life (Table 13); there was no association between pre-existing depression and use of ED services (OR 0.93, 95% CI 0.79-1.08, Table 14). Chemotherapy use was also similar across groups, as 17% of the depressed and 20% of the non-depressed subjects received chemotherapy in the last 30 days of life (Table 15); we found no significant association between pre-existing depression and chemotherapy receipt (OR 0.92, 95% CI 0.75-1.13, Table 16).

Sensitivity analysis

Using a more restrictive definition of depression, the percentage of subjects classified as having pre-existing depression decreased from 14% to 6% (n=966) of the study population. We found similar results, with no statistically significant association between pre-existing depression and inpatient admission (OR 0.94, 95% CI 0.79-1.12), emergency room visit (OR 0.86, 0.73-1.02), or chemotherapy receipt (OR 0.84, 95% CI 0.66-1.05). As in our primary analysis, we found lower odds of terminal admission (OR 0.76, 95%CI 0.62-0.93) and higher enrollment in hospice care (sub hazard ratio 1.17, 95% CI 1.05-1.29). In the sensitivity analysis, unlike in our primary analysis, we noted statistically significant lower odds of ICU admission (OR 0.75, 95% CI 0.61-0.92) among subjects with pre-existing depression.

Discussion

Recent research has focused on EOL care for cancer patients, since aggressive care may not be in accordance with patient or family wishes, and high intensity EOL care is a significant burden to health systems.[83,84] We characterized the impact of pre-existing depression on EOL care among older adults with metastatic NSCLC.

We found that a majority of advanced cancer patients utilize at least one form of aggressive EOL care, whether or not they have pre-existing depression. Pre-existing depression was associated with statistically significant higher use of hospice but was not associated with chemotherapy receipt, emergency room services, or inpatient admission in the last 30 days of life, after adjusting for age, gender, Klabunde comorbidity index, marital status, race, Hispanic ethnicity, Medicaid eligibility, and SEER registry.

Patient enrollment in hospice may be explained by unmeasured factors such as patient preferences or physician-patient relationship. As those with pre-existing depression had higher comorbidity scores, reflecting more illness, they likely had regular contact with their physicians. Such contact may in turn facilitate hospice entry, as physician factors have been found to be a significant factor predicting hospice enrollment. [85] Additionally, when patients discuss EOL care with a physician, they are more likely to receive care concordant with their wishes and understand their prognosis; patients who understand they are terminally ill are less likely to receive aggressive care. [86]

Some patients may not understand their prognosis and feel that cancer therapy portends cure,[87] even in the metastatic setting. This difference in attitude may influence the observed variation in hospice enrollment, with depressed patients less likely to assume a cure is possible, or more contact with treatment providers has allowed greater understanding of prognosis.

We found that subjects with pre-existing depression were statistically less likely to have a terminal admission, possibly due to enrollment in hospice care. These findings are similar to those from a randomized trial of early palliative care in lung cancer, where depression and anxiety at baseline were associated with chemotherapy at EOL but not hospitalization or emergency room use. [88] Another study noted that hospice enrollment among Medicare beneficiaries resulted in lower emergency room and hospitalizations at the end of life. [89]

We observed high use of aggressive EOL measures, a finding contrary to what many patients and families say they want at EOL.[90] Our findings indicate that health care provision at EOL may not provide sufficient support for patients and caregivers; additional resources and a restructuring of hospice may be needed to reduce aggressive EOL care. Since people with pre-existing depression enroll in hospice more often than those without depression, hospice providers have an additional burden of mental health care that may result in strain for hospice providers and indicate a need for additional resources while caring for people with advanced NSCLC at EOL.

Limitations

Patient and family preferences are determinants of end-of-life care, but as this is a retrospective claims-based analysis, we did not have access to information regarding preferences for intensity of health care, health care directives, or the results of EOL care discussions, that have been found to impact the intensity of EOL care. [91]

We did not have access to the results of any screening depression tests performed or patient response to antidepressant therapy to help confirm our classification of subjects as depressed or not depressed. It is possible that subjects may be not categorized properly if a depressive episode occurred before the one-year look back period of this study. Performance status has been associated with depression [50] and higher mortality [9,51] but performance status is unavailable in SEER-Medicare. There is an established association between depression and smoking, [43,52] both of which may predict negative patient outcomes, but smoking status is not available in the SEER-Medicare database.

The percentage of Medicare enrollees who had Part D coverage in the year before their diagnosis ranged from 48.8% in 2007 to 53.3% in 2013, [54] thus it is likely that we have not identified a number of people who were using antidepressants, and were not classified as depressed in this analysis.

Conclusion

Pre-existing depression is associated with higher enrollment in hospice care, and half of the study population used at least one measure of aggressive EOL care. Additional resources for hospice organizations and caregivers may help avoid the use of aggressive EOL care while addressing mental health needs among metastatic lung cancer patients.

Figure 1: Consort diagram for study population

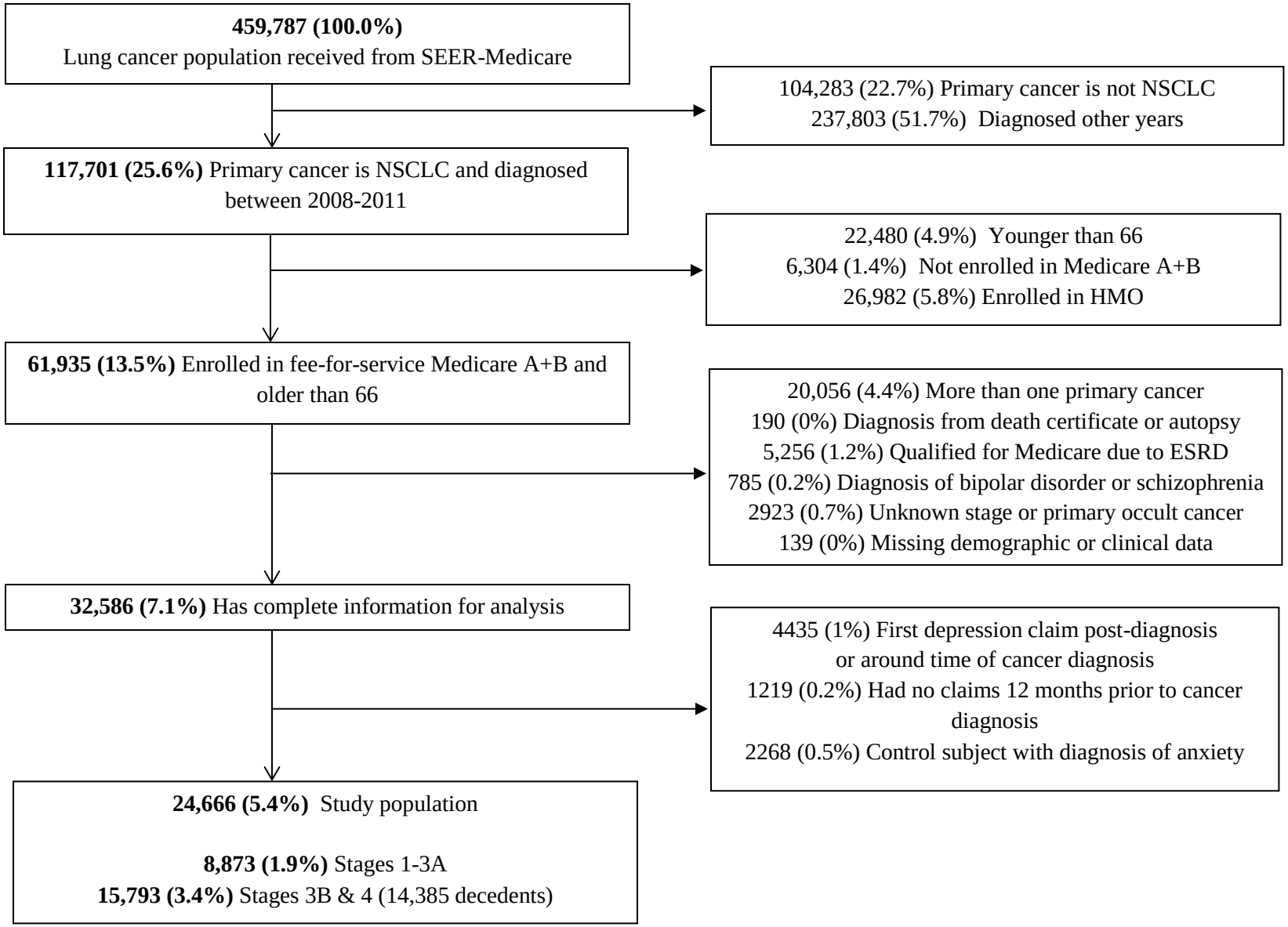

Table 1a. Demographics of study population to evaluate association between pre-existing depression and advanced stage (3B/4) at diagnosis. Distant depression=3 to 12 months before diagnosis using expanded depression criteria. Control group has no codes for depression or anxiety at any time. Total population size is 24,666.

	All stages		
	Lung cancer & distant depression n=3,949 (16%)	Lung cancer & no depression n=20,717 (84%)	P-value
Age (mean ± SD)	76.56 ± 6.87	76.97 ± 6.73	<0.001
Gender (n, %)			
Male	1274 (32%)	11392 (55%)	<0.001
Marital status			
Married	1565 (40%)	10966 (53%)	<0.001
Race			
White	3614 (92%)	17599 (85%)	<0.001
Hispanic ethnicity (n, %)	161 (4%)	830 (4%)	0.84
Klabunde (mean ± SD)	0.42 ± 0.46	0.26 ± 0.38	<0.001
Dual eligible (n, %)	625 (16%)	1798 (9%)	<0.001
Stage (n, %)			
1	1077 (27%)	4427 (21%)	<0.001
2	178 (5%)	940 (5%)	
3A	394 (10%)	1857 (9%)	
3B	682 (17%)	3606 (17%)	
4	1618 (41%)	9887 (48%)	
Residence (n, %)			
Metropolitan/Urban	3439 (87%)	18481 (89%)	<0.001
SEER registry*			
Northeast	753 (19%)	4148 (20%)	<0.001
Midwest	493 (12%)	2577 (12%)	
Southeast	1258 (32%)	5757 (28%)	
West	1445 (37%)	8235 (40%)	

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

Table 1b. Demographics of study population to evaluate association between pre-existing depression and receipt of anticancer therapy and survival. Distant depression=3 to 12 months before diagnosis using expanded depression criteria. Control group has no codes for depression or anxiety at any time. Total population size is 8,873.

	Stages 1-3A		
	Lung cancer & distant depression n=1649 (17%)	Lung cancer & no depression n=7224 (83%)	P-value
Age (mean ± SD)	76.01 ± 6.58	76.69 ± 6.44	<0.001
Gender (n, %)			
Male	505 (31%)	3895 (54%)	<0.001
Marital status			
Married	693 (42%)	3997 (55%)	<0.001
Race			
White	1520 (92%)	6249 (87%)	<0.001
Hispanic ethnicity (n, %)	58 (4%)	272 (4%)	0.63
Klabunde (mean ± SD)	0.43 ± 0.45	0.28 ± 0.37	<0.001
Dual eligible (n, %)	223 (14%)	585 (8%)	<0.001
Stage (n, %)			
1	1077 (65%)	4427 (61%)	0.005
2	178 (11%)	940 (13%)	
3A	394 (24%)	1857 (26%)	
3B	N/A	N/A	
4	N/A	N/A	
Residence (n, %)			
Metropolitan/Urban	1433 (87%)	6445 (89%)	0.007
SEER registry*			
Northeast	333 (20%)	1557 (22%)	0.022
Midwest	182 (11%)	823 (11%)	
Southeast	542 (33%)	2096 (29%)	
West	592 (36%)	2748 (38%)	

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

Table 2. Association of depression with advanced stage (3B/4) at diagnosis

	Odds ratio (95% CI)
Pre-existing depression	0.756 (0.676-0.846)
Age	1.011 (1.007-1.015)
Female gender	0.867 (0.820-0.917)
Non-married status	1.184 (1.119-1.252)
Non-white race	1.172 (1.082-1.270)
Hispanic ethnicity	1.103 (0.959-1.267)
Klabunde index	0.813 (0.760-0.869)
Pre-existing anxiety	0.875 (0.727-1.052)
Medicare-Medicaid enrollee	1.095 (0.996-1.203)
Rural residence	1.028 (0.941-1.124)
SEER registry**	
Midwest	1.288 (1.169-1.419)
Southeast	1.045 (0.965-1.132)
West	1.158 (1.077-1.246)
Antidepressants before diagnosis***	
1-180 days	1.107 (0.948-1.292)
180 days+	1.108 (0.941-1.248)

Comparison categories for analysis: *0-5% poverty; **Northeast SEER registry, ***no SSRI, SNRI, bupropion or mirtazapine.

Table 3. Receipt of anticancer therapy and days to therapy among subjects with stages 1-3A NSCLC

	Stage 1			Stage 2			Stage 3A		
	Depression (n=1077)	No depression (n= 4,427)	P-value	Depression (n=178)	No depression (n=940)	P-value	Depression (n=394)	No depression (n=1,857)	P-value
Chemotherapy only	54 (5%)	144 (3%)	0.01	7 (4%)	41 (4.5%)	0.80	40 (10%)	188 (10%)	0.99
Surgery only	432 (40%)	1891 (43%)	0.12	27 (15%)	125 (13%)	0.50	13 (3%)	50 (3%)	0.51
Radiation only	188 (18%)	635 (15%)	0.01	18 (10%)	86 (9%)	0.69	53 (13%)	203 (11%)	0.15
Chemotherapy & radiation	106 (10%)	456 (10.5%)	0.66	39 (22%)	191 (20.5%)	0.63	152 (39%)	768 (41.5%)	0.31
Chemotherapy & surgery	74 (7%)	391 (9%)	0.04	35 (20%)	197 (21%)	0.70	14 (4%)	96 (5%)	0.18
Surgery & radiation	42 (4%)	149 (3.5%)	0.39	4 (2%)	50 (5%)	0.08	5 (1%)	22 (1%)	0.89
Chemotherapy, radiation & surgery	37 (3%)	219 (5%)	0.04	19 (11%)	146 (16%)	0.09	35 (9%)	190 (10%)	0.42
No surgery, chemotherapy or radiation	144 (13%)	542 (12%)	0.32	29 (16%)	104 (11%)	0.04	82 (21%)	340 (18.5%)	0.25

Table 4. Median and range of days to anticancer therapy among subjects with stages 1-3A NSCLC

	Stage 1		Stage 2		Stage 3A	
	Depression (n=1077)	No depression (n= 4,427)	Depression (n=178)	No depression (n=940)	Depression (n=394)	No depression (n=1,857)
Median days to first anticancer therapy	40	41	42.5	47	42.5	42
Interquartile range	14-69	15-68	19-67	23-72	7-72	15-69

Table 5. Time to anticancer therapy, accounting for competing risk of death, among subjects with stage 1-3A NSCLC

	Stage 1	Stage 2	Stage 3A
	SHR (95% CI)	SHR (95% CI)	SHR (95% CI)
Pre-existing depression	0.979 (0.865-1.107)	0.834 (0.620-1.120)	0.813 (0.661-1.001)
Anxiety	1.042 (0.914-1.187)	1.099 (0.751-1.607)	1.304 (1.043-1.630)
Age	0.968 (0.964-0.973)	0.965 (0.955-0.975)	0.972 (0.964-0.979)
Female gender	1.099 (1.034-1.169)	1.067 (0.928-1.228)	1.026 (0.930-1.133)
Non-married status	0.834 (0.785-0.887)	0.785 (0.685-0.899)	0.826 (0.748-0.912)
Non-white race	0.817 (0.745-0.896)	0.914 (0.769-1.085)	0.989 (0.861-1.135)
Hispanic ethnicity	0.994 (0.865-1.142)	1.016 (0.736-1.402)	1.061 (0.824-1.366)
Klabunde index	0.890 (0.825-0.959)	0.842 (0.698-1.014)	0.725 (0.640-0.821)
Dual eligible	0.954 (0.861-1.056)	0.846 (0.682-1.051)	0.876 (0.735-1.043)
Rural residence	0.882 (0.796-0.977)	0.847 (0.676-1.061)	0.876 (0.741-1.036)
SEER registry**			
Midwest	0.864 (0.783-0.954)	0.945 (0.755-1.182)	0.966 (0.818-1.140)
Southeast	0.852 (0.780-0.929)	1.077 (0.891-1.301)	1.034 (0.905-1.181)
West	0.806 (0.745-0.872)	0.989 (0.829-1.181)	0.895 (0.792-1.011)
Antidepressants before diagnosis			
1-180 days	0.884 (0.745-1.049)	1.073 (0.714-1.614)	1.054 (0.809-1.373)
180 days+	0.953 (0.829-1.096)	1.232 (0.850-1.786)	1.156 (0.914-1.460)

Table 6. Days survived by depression classification among subjects with stages 1-3A NSCLC

	Distant depression (n=1649)	**No depression (n=7224)**
Stage 1	*(stage 1 n=1077)*	*(stage 1 n=4427)*
Median days survived	883	975
Interquartile range	328-1370	463-1460
Stage 2	*(stage 2 n=178)*	*(stage 2 n=940)*
Median days survived	510.5	676.5
Interquartile range	203-914	284-1160
Stage 3a	*(stage 3A n=394)*	*(stage 3A n=1857)*
Median days survived	366	362
Interquartile range	143-798	152-838

Table 7. Mortality risk among subjects with stages 1-3A NSCLC

	Stage 1	Stage 2	Stage 3A	All stages
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Pre-existing depression	1.193 (1.008-1.413)	1.301 (0.915-1.849)	1.137 (0.916-1.411)	1.147 (1.014-1.297)
Anxiety	0.752 (0.620-0.912)	0.951 (0.618-1.464)	0.698 (0.547-0.891)	0.738 (0.640-0.850)
Age	1.049 (1.042-1.056)	1.034 (1.020-1.047)	1.023 (1.015-1.031)	1.035 (1.030-1.040)
Female gender	0.668 (0.610-0.732)	0.743 (0.625-0.882)	0.869 (0.781-0.966)	0.720 (0.676-0.768)
Non-married status	1.188 (1.084-1.302)	1.142 (0.965-1.351)	1.119 (1.006-1.245)	1.158 (1.087-1.235)
Non-white race	0.901 (0.787-1.030)	0.931 (0.723-1.198)	0.988 (0.853-1.145)	0.958 (0.874-1.050)
Hispanic ethnicity	1.139 (0.915-1.418)	1.019 (0.638-1.627)	1.211 (0.945-1.552)	1.131 (0.969-1.320)
Klabunde index	1.919 (1.748-2.107)	1.755 (1.433-2.149)	1.535 (1.364-1.729)	1.678 (1.567-1.798)
Dual eligible	1.086 (0.937-1.258)	1.066 (0.810-1.402)	1.096 (0.925-1.300)	1.107 (0.999-1.227)
Rural residence	1.046 (0.914-1.196)	1.316 (1.021-1.697)	1.067 (0.904-1.260)	1.060 (0.963-1.167)
SEER registry**				
Midwest	1.396 (1.189-1.640)	1.034 (0.778-1.373)	0.961 (0.801-1.153)	1.135 (1.017-1.267)
Southeast	1.696 (1.485-1.938)	1.164 (0.923-1.469)	0.984 (0.853-1.135)	1.316 (1.204-1.439)
West	1.124 (1.096-1.411)	0.946 (0.757-1.182)	0.941 (0.822-1.075)	1.028 (0.945-1.119)
Antidepressants before diagnosis				
1-180 days	1.062 (0.847-1.332)	0.997 (0.622-1.600)	1.059 (0.810-1.383)	1.111 (0.947-1.305)
180 days+	1.189 (0.974-1.453)	0.834 (0.548-1.269)	1.117 (0.863-1.444)	1.142 (0.986-1.323)
Anticancer therapy	0.289 (0.246-0.339)	0.198 (0.138-0.284)	0.274 (0.226-0.334)	0.269 (0.240-0.302)

Table 8: Demographics of study population evaluating end-of-life care for stages 3B and 4 with expanded depression definition. Distant depression=3 to 12 months before diagnosis. Control group has no codes for depression or anxiety at any time. Total population size represents 14,385 decedents.

	Lung cancer & distant depression n=2082 (14%)	Lung cancer & no depression N=12,303 (86%)	P-value
Age (mean ± SD)	77.17 ± 7.13	77.21 ± 6.89	0.82
Gender (n, %)			
Male	712 (34%)	6918 (56%)	<0.001
Marital status			
Married	769 (37%)	6287 (51%)	<0.001
Race			
White	1895 (91%)	10378 (84%)	<0.001
Hispanic ethnicity (n, %)	89 (4%)	508 (4%)	0.76
Klabunde (mean ± SD)	0.42 ± 0.47	0.26 ± 0.38	<0.001
Dual eligible (n, %)	370 (18%)	1131 (9%)	<0.001
Stage (n, %)			
3B	587 (28%)	3107 (25%)	0.01
4	1495 (72%)	9196 (75%)	
Residence (n, %)			
Metropolitan/Urban	1816 (87%)	10960 (89%)	0.01
SEER registry*			
Northeast	381 (18%)	2367 (19%)	<0.001
Midwest	284 (14%)	1618 (13%)	
Southeast	662 (32%)	3376 (27%)	
West	755 (36%)	4942 (40%)	

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

Table 9. Hospice service length among decedents with stage 3B or 4 NSCLC

	Depressed (n=2082)	**Not depressed** (n=12303)
Patients utilizing hospice at anytime	1431 (69%)	7754 (63%)
Days enrollment prior to death among hospice users		
0-3 days	298 (21%)	1713 (22%)
4-7 days	213 (15%)	1178 (15%)
8-30 days	460 (32%)	2575 (33%)
31-60 days	188 (13%)	1079 (14%)
Greater than 60 days	272 (19%)	1209 (16%)

Table 10. Time to hospice enrollment among subjects with stage 3B or 4 NSCLC

	SHR (95% CI)
Pre-existing depression	1.163 (1.055-1.281)
Age	1.022 (1.019-1.026)
Female gender	1.137 (1.088-1.188)
Non-married status	1.061 (1.015-1.110)
Non-white race	0.782 (0.733-0.835)
Hispanic ethnicity	0.979 (0.874-1.097)
Klabunde index	0.878 (0.829-0.930)
Dual eligible	0.925 (0.856-0.999)
Anxiety	1.007 (0.895-1.133)
Rural residence	0.853 (0.794-0.916)
SEER registry**	
Midwest	1.438 (1.338-1.546)
Southeast	1.325 (1.242-1.412)
West	1.021 (0.963-1.084)
Antidepressants before diagnosis	
1-180 days	1.051 (0.924-1.196)
180 days+	0.974 (0.864-1.098)

Comparison categories for analysis: *0-5% poverty; **Northeast SEER registry, *** no SSRI, SNRI, bupropion or mirtazapine.

Table 11. Inpatient, ICU, and terminal admissions in last month of life among subjects with 3b/4 NSCLC

	Depressed (n=2082)	**Not depressed** (n=12303)
Inpatient admissions		
None	885 (42%)	5207 (42%)
1	804 (39%)	4732 (38%)
2	285 (14%)	1730 (14%)
3	80 (4%)	515 (4%)
4 or more	28 (1%)	119 (1%)
ICU admissions		
None	1639 (79%)	9402 (76%)
1	402 (19%)	2606 (21%)
2	36 (2%)	275 (2%)
3 or more	5 (<1%)	20 (<1%)
Terminal admissions	487 (23%)	3364 (27%)

Table 12. Association of depression and inpatient admission, ICU admission, and terminal admission in the last 30 days of life for decedents with stage 3B/4 NSCLC

	Inpatient admissions Odds ratio (95% CI)	**ICU admissions** Odds ratio (95% CI)	**Terminal admissions** Odds ratio (95% CI)
Pre-existing depression	1.046 (0.894-1.224)	0.849 (0.703-1.025)	0.762 (0.633-0.916)
Age	0.988 (0.983-0.993)	0.980 (0.974-0.986)	0.988 (0.982-0.993)
Female gender	0.843 (0.785-0.906)	0.851 (0.783-0.926)	0.867 (0.800-0.939)
Non-married status	0.989 (0.920-1.063)	0.956 (0.879-1.039)	0.946 (0.8730-1.025)
Non-white race	1.295 (1.171-1.431)	1.289 (1.155-1.439)	1.471 (1.325-1.632)
Hispanic ethnicity	1.228 (1.031-1.462)	1.140 (0.940-1.382)	1.108 (0.921-1.333)
Klabunde index	1.572 (1.439-1.717)	1.688 (1.537-1.854)	1.480 (1.357-1.622)
Dual eligible	1.097 (0.975-1.233)	1.218 (1.070-1.386)	1.262 (1.116-1.427)
Anxiety	0.967 (0.791-1.182)	0.932 (0.729-1.192)	0.884 (0.696-1.124)
Rural residence	0.981 (0.876-1.098)	0.788 (0.683-0.909)	1.256 (1.105-1.428)
SEER registry**			
Midwest	0.823 (0.728-0.931)	0.875 (0.760-1.007)	0.521 (0.452-0.602)
Southeast	0.667 (0.600-0.741)	0.754 (0.667-0.852)	0.659 (0.586-0.741)
West	0.698 (0.634-0.768)	0.934 (0.839-1.041)	0.900 (0.813-0.997)
Antidepressants before diagnosis			
1-180 days	0.796 (0.620-0.975)	0.982 (0.770-1.253)	0.985 (0.777-1.249)
180 days+	0.964 (0.794-1.172)	1.031 (0.816-1.304)	1.189 (0.947-1.492)

Comparison categories for analysis: *0-5% poverty; **Northeast SEER registry, *** no SSRI, SNRI, bupropion or mirtazapine.

Table 13. Emergency room utilization in last 30 days of life among subjects with 3B/4 NSCLC

	Depressed (n=2082)	**Not depressed** (n=12303)
Any emergency room visit	1051 (50%)	6343 (52%)
Number of ER visits		
None	1031 (50%)	5960 (48%)
1	818 (39%)	4808 (39%)
2	203 (10%)	1278 (10%)
3 or more	30 (1%)	257 (3%)
Mean number of ER visits (±SD)	0.63 ± 0.73	0.66 ± 0.76

Table 14. Association of depression and at least 1 emergency room visit within 30 days of death for decedents with stage 3B/4 NSCLC

	ER visit Odds ratio (95% CI)
Pre-existing depression	0.925 (0.792-1.080)
Age	0.990 (0.985-0.995)
Female gender	0.830 (0.774-0.891)
Non-married status	0.971 (0.904-1.042)
Non-white race	1.337 (1.212-1.475)
Hispanic ethnicity	1.123 (0.947-1.332)
Klabunde index	1.349 (1.239-1.469)
Anxiety	1.093 (0.896-1.333)
Medicaid-Medicare enrollee	1.200 (1.069-1.347)
Rural residence	0.945 (0.845-1.057)
SEER registry**	
Midwest	0.857 (0.760-0.966)
Southeast	0.649 (0.585-0.719)
West	0.714 (0.650-0.784)
Antidepressants before diagnosis	
1-180 days	0.944 (0.772-1.154)
180 days+	1.066 (0.879-1.291)

Comparison categories for analysis: *0-5% poverty; **Northeast SEER registry, *** no SSRI, SNRI, bupropion or mirtazapine.

Table 15. Chemotherapy use in last 30 days of life among subjects with stage 3B/4 NSCLC

	Depressed (n=2082)	**Not depressed** (n=12303)
Any chemotherapy use in last 30 days of life	357 (17%)	2486 (20%)
Timing of utilization among those receiving chemotherapy		
IV chemotherapy, last 30 days	334 (94%)	2287 (92%)
IV chemotherapy, last 14 days	185 (52%)	1240 (50%)
Oral chemotherapy, last 30 days	27 (8%)	228 (9%)

Table 16. Association of pre-existing depression and chemotherapy use in the last 30 days of life among subjects with stages 3B/4 NSCLC

	Chemotherapy Odds ratio (95% CI)
Pre-existing depression	0.923 (0.753-1.131)
Age	0.953 (0.947-0.960)
Female gender	0.956 (0.875-1.044)
Non-married status	0.719 (0.658-0.786)
Non-white race	0.962 (0.851-1.088)
Hispanic ethnicity	0.927 (0.746-1.153)
Klabunde index	0.840 (0.750-0.940)
Anxiety	1.025 (0.789-1.330)
Medicare-Medicaid enrollee	1.023 (0.883-1.185)
Rural residence	0.969 (0.841-1.117)
SEER registry**	
Midwest	0.930 (0.801-1.081)
Southeast	0.821 (0.721-0.935)
West	0.933 (0.831-1.049)
Antidepressants before diagnosis	
1-180 days	0.815 (0.618-1.075)
180 days+	0.962 (0.747-1.239)

Comparison categories for analysis: *0-5% poverty; **Northeast SEER registry, *** no SSRI, SNRI, bupropion or mirtazapine.

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