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Associations of Pre- and Post-Cancer Depression With End-of-Life Cancer Care Intensity

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Background

Depression has adverse effects on health outcomes and the quality of end-of-life care among cancer patients. However, overly aggressive EOL care can result in high costs and may not be consistent with patient preferences or linked to better health. As such, there is rising interest in identifying the associations between depression and care quality for cancer patients. This study investigates whether depression is associated with EOL care intensity among elderly individuals with cancer.

Methods

Utilizing the Surveillance, Epidemiology, and End Results-Medicare linked database, we identified decedents aged 66 years or older either with pre-cancer depression, post-cancer depression, or no depression at all. All participants were diagnosed with cancer from 2004-2011 and died within 3 years as a result of cancer. Using hierarchical generalized linear models, we determined the associations of pre- and post-cancer depression on EOL care intensity, adjusting for sociodemographic and clinical characteristics.

Results

Our sample consisted of 84,947 Medicare beneficiaries, of whom 5,072 (6%) had pre-cancer depression and 6,677 (7.9%) had post-cancer depression. Compared to participants without depression, those with pre-cancer depression were significantly less likely to have repeated hospitalizations (adjusted odds ratio [AOR] = 0.91, 95% confidence interval [CI] = 0.83-0.99) or emergency department visits (AOR = 0.89, 95% CI = 0.83-0.94), experience in-hospital death (AOR = 0.83, 95% CI = 0.77-0.89), and receive intensive care unit services (AOR = 0.86, 95%

CI = 0.79-0.93) or late chemotherapy (AOR = 0.83, 95% CI = 0.70-0.99), and more likely to use hospice care (AOR = 1.20, 95% CI = 1.12-1.28). Participants with post-cancer depression had similar care intensity patterns as those with pre-cancer depression, but were insignificantly more likely to have repeat hospitalizations than those without depression (AOR = 1.04, 95% CI = 0.97-1.12).

Conclusions

Participants with pre- or post-cancer depression were less likely to receive aggressive EOL care than those without depression. Our findings suggest understanding the mechanisms that lead to these patterns may enhance EOL care quality for patients with cancer. Accurate screening and treatment for depressed patients in addition to earlier communication and initiation of hospice for all cancer patients can help promote palliative care.

Keywords: cancer, depression, end-of-life care, intensity, oncology

Introduction

There is rising interest in identifying the associations between depression and end-of-life (EOL) care intensity for patients with cancer.[1, 2] Previous research shows that cancer patients have an increased risk of depression compared to the general population.[3-7] The prevalence of depression is high in patients with terminal illnesses like cancer,[8, 9] where estimates vary that 15% to 50% of patients with cancer will experience depressive symptoms.[7, 9-12] Because depression is among one of the leading causes of disability globally, it has major implications for health outcomes and quality of life among affected individuals.[9] These repercussions consist of adverse effects on functional status, health-related quality of life, health care use, and medical costs.[13-15] Several studies indicate co-occurring depression and cancer may impact the morbidity of patients such that those with depression and cancer are less likely to adhere to treatment regimens and more likely to have other comorbidities and prolonged hospital stays compared to patients without depression; these factors can lead to increased health care utilization, high expenditures, and more aggressive EOL cancer care.[1, 3, 14, 16]

Case in point, EOL care constitutes a disproportionate amount of Medicare costs, accounting for more than one-fourth of the spending on the elderly in the last year of life.[17, 18] In addition, overly aggressive EOL care may not be consistent with patient wishes or associated with better health and quality of life.[19-21] While studies have examined the effects of depression on cancer patients in terms of health care utilization and expenditures, there is a dearth of literature investigating the associations of pre- or post-cancer depression with EOL care intensity among adults with cancer. Available research examining depression and EOL care among those with cancer is limited in both study scope and sample size[3, 22-24] or unclear in its diagnostic criteria for depression.[16] That is, it is not clear if depression preceded or followed the cancer

diagnosis. One study found that in adult cancer patients (≥21 years), depression is associated with higher health care utilization and expenditures, but the window of time for a depression diagnosis was not defined.[16] Three studies investigating elderly patients with a certain type of cancer, either breast, colorectal, or pancreatic, determined that pre-cancer depression is associated with a decrease in EOL care intensity.[3, 22, 24] Conversely, a study examining the prevalence and cumulative expenditures of post-cancer depression on patients with prostate cancer (>65 years) determined depression during the treatment phase was correlated with significant health resource utilization, expenses, and mortality.[23] The evidence so far is inconclusive. Potential explanations include: 1) the timeframe in which depression occurs, either prior to or after a cancer diagnosis, may affect participants' EOL cancer care differently, and 2) there is also a possibility that different types of cancer are influencing these effects. This issue is important to investigate on a more comprehensive scale, as EOL care costs are exorbitant.

To our knowledge, previous studies have not concomitantly evaluated differences in the quality and intensity of EOL care with cancer patients' psychological well-being across the mental health spectrum, such as depression both prior to and after cancer diagnosis. It is probable elderly patients with cancer may be less likely to seek care when ill as a result of depression,[22] but it is not known whether they have significantly different patterns of health care utilization and costs compared to those without depression. We hypothesize that patients with pre- or post-cancer depression will be less likely to receive aggressive EOL cancer care than those without depression. To address this knowledge gap, we investigated whether depression is associated with differences in EOL care intensity patterns over time in a population-based cohort of Medicare beneficiaries who had died from cancer, incorporating a comprehensive range of cancer types and criteria for the different depression groups. We then analyzed the associations

between depression and EOL care intensity patterns after controlling for sociodemographic, health status, and market variables. Understanding how mental illness may be correlated with EOL care for cancer patients can help expand current knowledge on the underlying mechanism leading to these differences and has potential implications for policy and action. Evidence of a relationship between a pre- or post-cancer diagnosis of depression and subsequent EOL care quality for adults with terminal cancers might also identify a select group for whom mental health services may be most needed or support earlier communication and initiation of hospice care, among other palliative care options, for patients.

Methods

Data source and study design

For this retrospective cohort analysis, we utilized the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, a unique population-based data source that links Medicare enrollment and claims to cancer registries from the time of a beneficiary's Medicare eligibility until date of death.[25] To date, the SEER cancer registries encompass approximately 30% of the United States population, collecting information on cancer incidence and survival.[25] We used SEER data to identify patient sociodemographic and cancer tumor characteristics for our sample. We used Medicare inpatient and outpatient claims to determine all covered health care services and categorize the depression diagnosis corresponding to each Medicare beneficiary who had died from cancer. The Yale Human Investigation Committee determined that this research study did not directly involve human subjects.

Patients

We identified elderly Medicare fee-for-service decedents who had breast, prostate, lung, colorectal, pancreatic, liver, kidney, melanoma, or hematological cancer diagnosed during 2004-2011 and who died within 3 years of cancer diagnosis by December 2011 as a result of it. Because Medicare claims were used to identify patients with a pre-cancer diagnosis of depression in the year before cancer diagnosis, the study population was restricted to patients who were 66 years or older at cancer diagnosis and who were continuously enrolled in Medicare Parts A and B for at least 12 months before cancer diagnosis through death. This provides a minimum of 12 months of Medicare claims data to ascertain depression. Patients were excluded from our analyses if their cancer diagnosis occurred solely according to death certificates or autopsy claims, if they lived less than 6 months after cancer diagnosis, or if their income or education by zip code information was unknown.

Key dependent variables

Outcomes of interest examined include 6 EOL care intensity measures developed by Earle et al.: >1 hospitalization within 30 days of death, >1 emergency department (ED) visit within 30 days of death, ≥1 intensive care unit (ICU) admission within 30 days of death, in-hospital death, any hospice use within 180 days of death, and chemotherapy received within 14 days of death.[26, 27] These data were gathered from Medicare claims.

Key independent variable

The primary independent variable examined in this study was depression. We identified the presence of depression among participants based on a search for depression diagnoses in all inpatient and outpatient Medicare claims data according to International Classification of

Diseases (ICD)-9 diagnostic codes 296.2, 296.3, 296.5, 296.6, 296.7, 298.0, 301.10, 301.12, 301.13, 309.0, 309.1 and 311.[3] These depression diagnoses looked at primary and secondary codes for major depressive disorder, bipolar disorder, affective personality disorder, and other medically relevant depressive symptoms; previous studies on depression and cancer have examined this set of ICD-9 codes.[3, 22, 24] Patients are identified as having a diagnosis of depression if they had at least one claim with at least one of the ICD-9 codes.[28] The timeframe for a pre-cancer depression diagnosis includes 12 months of Medicare claims that cancer decedents have upon enrollment at age 65. We thus categorized pre-cancer depression as occurring at any point during the 12-month period prior to cancer diagnosis, where individuals with pre-cancer depression can be either with or without post-cancer depression. Individuals with post-cancer depression are categorized as only having depression during the 6-month period after cancer diagnosis. Individuals with no depression at all do not have Medicare claims with the designated ICD-9 depression codes prior to or after their cancer diagnosis.

Other covariates

Baseline patient characteristics included race, age, gender, marital status, metropolitan status of residence, comorbidity, and disability status. The SEER-Medicare database also allows for census-based estimates of the median household income and the percentage of adults with a high school education or less at the zip code level. We used modified Charlson comorbidity conditions created for Medicare claims data to determine the degree of comorbidity per participant.[29] This adaptation is based on an approach that requires the diagnostic code appear on either inpatient or outpatient Medicare claims data in the year prior to the cancer diagnosis; depression was excluded from the Charlson comorbidity index analysis because it is our

exposure variable of interest.[22, 24, 30] Patients were categorized as having 0, 1 to 2, or more than 3 comorbidities. A disability index, which serves as a multivariate claim-based indicator for services commonly needed by older patients with poor or functional performance, was also added.[31] Tumor characteristics included tumor site, advanced stage of cancer (yes or no), multiple cancers (yes or no), and duration between cancer diagnosis and death (6 months-1 year, 1-2 years, 2-3 years), as reported by the SEER cancer registries.

Statistical analysis

Sociodemographic and tumor characteristics participants were summarized using mean (SD) for continuous variables and percentages for categorical variables. We used t-tests to compare the continuous age variable and Pearson chi-square tests to compare categorical patient sociodemographic and tumor characteristics between the different depression groups. Associations were observed between decedents with pre-cancer depression and those without depression, and between decedents with post-cancer depression and those without depression. To examine the unadjusted associations between depression diagnosis and our EOL care intensity outcomes of interest, we carried out additional Pearson chi-square tests.

In multivariate analyses, we constructed 2-level hierarchical generalized linear models (HGLMs), clustering patients by hospital referral region (HRR), to investigate whether pre- or post-cancer depression compared to no depression might significantly account for the variation in EOL care intensity among cancer decedents. The conservative results provided by HGLMs were used to examine the adjusted associations between depression and EOL care intensity. Adjusted odds ratios (AOR) and 95% confidence intervals (CI) were estimated after adjustment for possible confounding variables such as patient demographics, clinical factors, and market

factors. In addition, we tested to see whether there are statistically significant interactions of depression with cancer type, race, and income on EOL care intensity. For all analyses, the reference group is comprised of participants with cancer but no depression either prior to or after cancer diagnosis in the timeframes previously mentioned. Statistical significance was set at $p<0.05$. All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Results

Description of the study sample

The sample consisted of 84,947 elderly Medicare beneficiaries reported with cancer during 2004-2011. 5,072 patients (6.0%) had pre-cancer depression whereas 6,677 patients (7.9%) had post-cancer depression. Bivariate associations of patient characteristics with either pre- or post-cancer depression to the reference group with no depression are shown in **Table 1**. The mean age of participants without depression was lower than that of participants with pre-cancer depression (78.3 vs. 78.6, $p<0.05$), but higher than that of participants with post-cancer depression (78.3 vs. 77.8, $p<0.001$). In comparison to participants with no depression, those with either pre- or post-cancer depression were significantly more likely to be non-Hispanic white, male, and unmarried ($p<0.001$ for all). Participants with pre- or post-cancer depression also tended to have more comorbidities and a worse disability index than those without depression ($p<0.001$). However, decedents with pre- or post-cancer depression were significantly less likely to have multiple cancers than those without depression ($p<0.001$). When examining the months alive since cancer diagnosis, there were significantly lower percentages of participants with pre- or post-cancer depression compared to those without depression in the 1-2 years and 2-3 years categories ($p<0.001$ for all).

Depression and unadjusted differences in EOL care patterns

Unadjusted associations between depression diagnosis and care intensity within our sample of cancer decedents are displayed in **Figure 1**. Participants with pre- or post-cancer depression were significantly less likely to receive ICU services in the last 30 days or late chemotherapy in the last 14 days of life than participants without depression (p<0.001 for both). Participants with pre- or post-cancer depression were also significantly less likely to experience in-hospital death than those without depression (p<0.001 for decedents with pre-cancer depression, p=0.001 for decedents with post-cancer depression). Participants with pre- or post-cancer depression appear to have lower rates of repeat ED visits (p<0.05 for decedents with pre-cancer depression, p=0.215 for decedents with post-cancer depression) and were significantly more likely to use hospice care in the last 180 days of life than their non-depressed counterparts (p<0.001). Patients with pre-cancer depression were less likely to have repeat hospitalizations (p=0.126) whereas patients with post-cancer depression were more likely to have repeat hospitalizations than their non-depressed counterparts (p=0.074); however, these results were statistically insignificant.

Adjusted associations between depression and EOL care patterns

The results of multivariate analyses from AORs and 95% CIs of pre- or post-cancer depression on EOL care intensity indicators are summarized in **Table 2**. As predicted, pre-cancer depression and post-cancer depression were associated with significantly lower rates of ICU use, in-hospital death, and late chemotherapy. Compared to decedents without depression, decedents with pre-cancer depression were significantly less likely to have repeated hospitalizations (AOR = 0.91, 95% CI = 0.83-0.99) or ED visits (AOR = 0.89, 95% CI = 0.83-0.94), experience in-

hospital death (AOR = 0.83, 95% CI=0.77-0.89), and receive ICU services (AOR = 0.86, 95% CI = 0.79-0.93) or late chemotherapy (AOR=0.83, 95% CI=0.70-0.99). However, decedents with pre-cancer depression were more likely to use hospice care than decedents without depression (AOR = 1.20, 95% CI = 1.12-1.28). Participants with post-cancer depression had similar EOL care intensity patterns to those with pre-cancer depression, but were insignificantly more likely to have repeat hospitalizations than their counterparts without depression (AOR = 1.04, 95% CI = 0.97-1.12). In addition, we did not find significant interactions of depression with cancer type, race, and income on EOL cancer care intensity (p>0.05).

Discussion

We determined the associations between depression and EOL care intensity among Medicare fee-for-service beneficiaries who died as a result of cancer. Our findings indicate that across various EOL care intensity indicators, participants with pre- or post-cancer depression tended to receive less aggressive EOL cancer care and were more likely to utilize hospice care compared to those without depression. These results are consistent with earlier studies that established depression is correlated with lower odds of receiving definitive treatment among cancer patients.[3, 22]

Our findings build upon previous work in important ways. First, our research links depression, be it a pre- or post-cancer diagnosis of depression, with EOL cancer care aggressiveness over a longitudinal period of time. There have been no studies conducted to our knowledge that examined both pre- and post-cancer depression within the same study population. Previous research studies have investigated EOL cancer care patterns and expenditures either with pre-cancer depression alone or post-cancer depression alone, but those

findings were inconsistent. We did not find existing definitive conclusions about the associations of EOL care aggressiveness or quality for elderly participants with cancer and co-occurring depression. Our findings therefore provide a comprehensive view of EOL cancer care intensity patterns and depression among cancer decedents, whether they have pre-cancer depression, post-cancer depression, or no depression at all.

Secondly, instead of concentrating on a single cancer type, our research incorporates a broader range of cancer types than other studies, offering an all-inclusive understanding of the effects of depression on older patients with terminal cancer. Our study is strengthened by the large sample size and is adequately powered to detect statistically significant differences between depressed (prior to or after cancer diagnosis) and non-depressed cancer patients. We accordingly evaluated common terminal cancers among elderly adults, including breast, prostate, lung, colorectal, pancreatic, liver, kidney, melanoma, and hematological cancer. However, our results differ from previous studies that demonstrated associations between depression and greater EOL care aggressiveness with higher health care utilization.[16, 23] These differences are plausible given that the onset of depression may vary by age, gender, or cancer type. Different types of cancer have distinct prevalence rates of depression, which may influence EOL care intensity. For example, the prevalence of depression was reported as 38% in pancreatic cancer patients, 14% to 40% in breast cancer patients, and 4.7% to 33% in lung cancer patients.[16] However, we did not find significant interactions between depression and cancer type, which suggests the robustness of our results. It is important that future research continue being conducted for specific types of cancer, depending on health priorities. Certain cancers may also lend themselves to different pathways and symptoms that could contribute to varying health care utilization trends. We

recommend that further understanding of the social or biological mechanisms that lead to these care patterns may enhance EOL care quality for all cancer patients.

Third, while our research identifies significant differences in EOL care intensity patterns between participants with pre- or post-cancer depression and those with no depression, we did not find statistically important interactions between depression and race or income. In our population-based study, pre- or post-cancer depression was a significant predictor of care intensity in participants. Even after controlling for characteristics such as income, a proxy for socioeconomic mobility and access to care, the associations remained significant. We have reason to believe that patient preferences may play a role in these EOL care patterns. In a study looking at the effects of pre-cancer depression on older women with breast cancer, researchers arrived at two possible hypotheses for the increased mortality patterns among depressed participants – depression causes the individual to be less capable of functioning properly in society and may also be an indicator of global brain dysfunction.[22] It is plausible that because the depressed cancer patient is less likely to seek care when ill or to adhere to medical regimens and treatments, these factors may contribute to lower rates of survival and health care utilization.[22] Patients who are diagnosed with depression and their providers may adopt a nihilistic attitude toward their illness, either due to depression or other negative aspects of their life, and thus would be unlikely to seek specialized care.[3, 22, 32] Patients with a pre- or post-cancer diagnosis of depression may also prefer a quality-enhancing approach that incorporates palliative care options like hospice. In contrast, aggressive EOL care in patients without depression may be consistent with patient preferences for a life-prolonging approach.

There were several limitations to our study. First, we acknowledge that accurate diagnosis of patients with depression is frequently underreported in administrative claims data.[33]

However, the rate of depression in our study sample (13.9%) falls within the established prevalence range of 5% to 20% for cancer patients diagnosed major depressive disorder and depressive symptoms comorbid with cancer,[10] supporting our findings. Because analyses are based on the SEER-Medicare fee-for-service beneficiary population, our findings include a considerable number of cases but may not necessarily characterize all Medicare beneficiaries in the United States. In addition to limited generalizability, we did not include patient preferences in our analyses because they are not known from Medicare claims data. While patient wishes have not been demonstrated to be a significant factor in expenditure variation at the end of life,[20] we believe physician behaviors may be a driving factor in the associations we observed between depression and EOL cancer care intensity. Future research examining patient experiences and physician practice behaviors with the associations between depression and EOL care intensity is needed. Finally, our retrospective study design may also limit our findings. Our population-based cohort is comprised of retrospective cancer decedents. Participants who had pre- or post-cancer depression but did not die during the window of time we chose would not be included in our analyses. Prospective research to confirm our retrospective research findings is therefore necessary.

In conclusion, our study demonstrates that pre-cancer depression and post-cancer depression are associated with lower EOL cancer care intensity and higher overall hospice care utilization among elderly patients with cancer. While the significantly higher rates of hospice care among participants with pre- or post-cancer depression are promising, our findings on less aggressive EOL care patterns among depressed patients should be interpreted with caution. Improving physician awareness of the high prevalence of depression comorbid with cancer and accurate screening and treatment for depressed patients can lessen the detrimental influence of

depression on health outcomes in cancer.[3] Earlier communication and initiation of hospice for all

patients can also help increase palliative care rates. More discussions among medical providers

on cancer and co-occurring mental illness can lead to improved protocols for depressed patients

who need appropriate mental health treatment and end-of-life care, especially among this elderly

cancer patient population. Such actions can potentially lower unnecessary utilization of health

care resources among elderly adults with cancer and promote better, more empathetic care that

aligns with patient preferences.

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Table 1. Selected patient characteristics, by depression diagnosis

	No Depression	Pre-Cancer Depression	P-Value*	Post-Cancer Depression	P-Value*
	N=73,198	N=5,072		N=6,677	
Race (%)			<0.001		<0.001
Non-Hispanic White	82.4	86.2		86.3	
African American	8.4	6.5		6.5	
Hispanic	4.5	5.0		4.6	
Asian	4.8	2.4		2.6	
Age in years (mean, SD)	78.3 (6.7)	78.6 (7.0)	0.002	77.8 (6.7)	<0.001
Female (%)			<0.001		<0.001
No	45.5	64.4		57.6	
Yes	54.5	35.6		42.4	
Marital Status (%)			<0.001		<0.001
Married	52.7	38.5		45.7	
Unmarried	42.4	56.2		49.7	
Unknown	4.9	5.3		4.6	
Metropolitan (%)			0.006		0.431
Metro	82.3	80.8		82.7	
Non-metro/Unknown	17.7	19.2		17.3	
Income (%)			<0.001		0.071
< $33,000	23.1	24.2		22.2	
$33,000 - $39,999	15.8	17.2		15.4	
$40,000 - $49,999	20.4	21.0		20.2	
$50,000 - $62,999	19.2	18.4		19.3	
≥ $63,000	21.5	19.2		22.9	
High School Education (%)			0.378		0.774
< 30%	21.3	20.3		21.2	
30% - 39%	15.5	15.4		15.9	
40% - 49%	17.3	18.1		17.7	
50% - 59%	18.7	19.1		18.4	
≥ 60%	27.2	27.1		26.9	
Comorbidity (%)			<0.001		<0.001
None	46.9	24.1		42.2	
1 to 2	38.5	43.0		40.9	
More than 3	14.7	32.9		16.9	
Disability Status (%)			<0.001		<0.001
No	92.5	70.8		87.1	
Yes	7.5	29.2		12.9	
Tumor Site (%)			<0.001		<0.001
Breast	7.4	10.6		7.5	
Prostate	7.8	4.3		4.4	
Lung	40.4	41.7		40.4	
Colorectal	14.5	14.5		17.5	
Pancreas	7.0	6.3		8.8	
Liver	2.7	2.3		1.8	
Kidney	3.3	3.1		3.0	
Skin	4.3	4.0		2.1	
Hematological cancer	12.6	13.1		14.6	
Stage IV at diagnosis (%)			<0.001		0.625
Not stage IV	69.1	74.2		68.8	
Stage IV	30.9	25.8		31.2	

Multiple cancers (%)			<0.001		<0.001
No	87.1	89.4		89.8	
Yes	12.9	10.6		10.2	
Duration between cancer diagnosis and death (%)			<0.001		<0.001
6 months - 1 year	36.8	41.6		47.0	
1 - 2 years	41.0	40.0		36.7	
2 - 3 years	22.1	18.4		16.4	

*: No depression as reference.

Figure 1. Differences in end-of-life care patterns, by depression diagnosis*
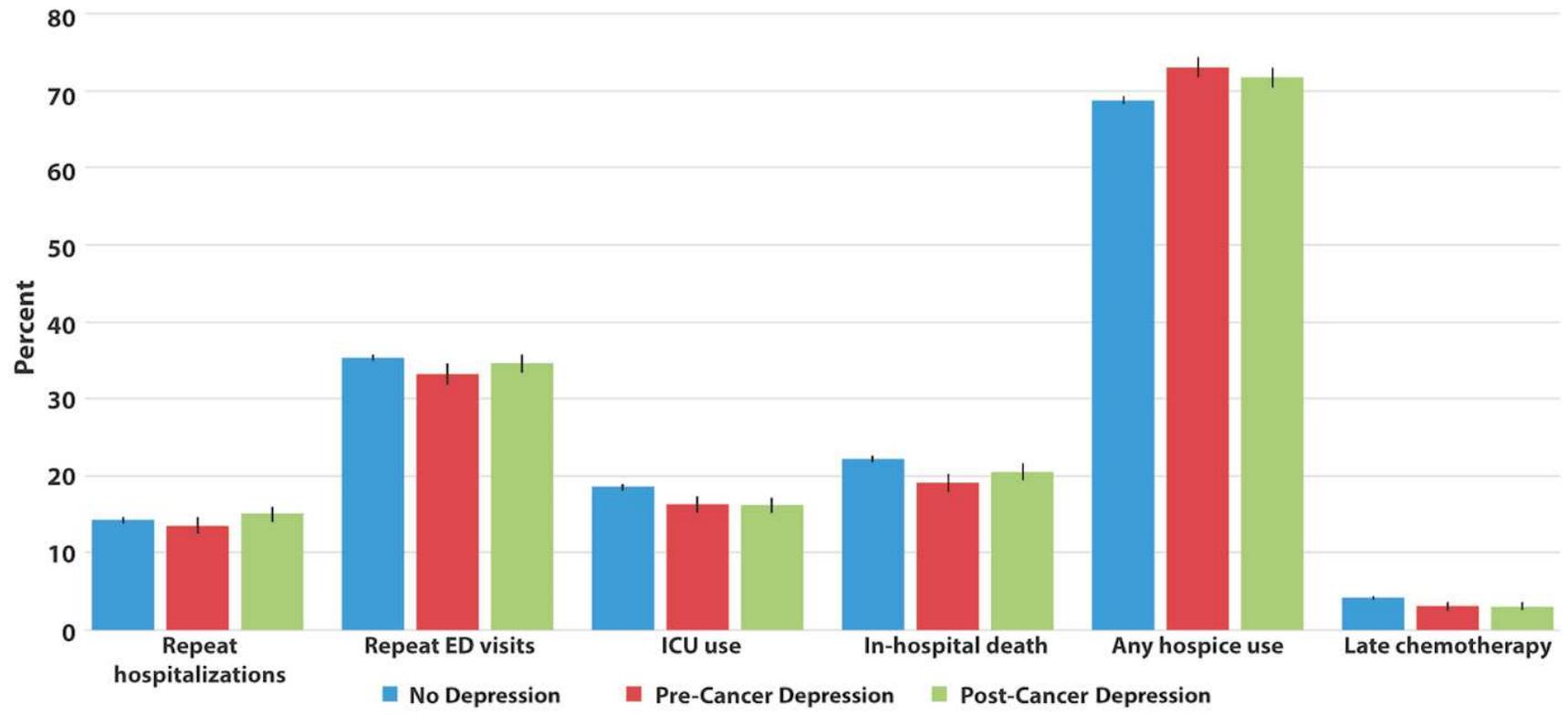
*: 95% confidence intervals are provided for each care intensity indicator, by depression diagnosis.

Table 2. Adjusted associations between depression diagnosis and EOL care patterns

	No Depression	Pre-Cancer Depression	Post-Cancer Depression
	N=73,198	N=5,072	N=6,677
Repeat hospitalizations			
Adjusted odds ratio (95% CI)*	Reference	**0.91 (0.83, 0.99)**	1.04 (0.97, 1.12)
Repeat ED visits			
Adjusted odds ratio (95% CI)*	Reference	**0.89 (0.83, 0.94)**	0.96 (0.91, 1.01)
ICU use			
Adjusted odds ratio (95% CI)*	Reference	**0.86 (0.79, 0.93)**	**0.84 (0.79, 0.91)**
In-hospital death			
Adjusted odds ratio (95% CI)*	Reference	**0.83 (0.77, 0.89)**	**0.89 (0.84, 0.95)**
Any hospice use			
Adjusted odds ratio (95% CI)*	Reference	**1.20 (1.12, 1.28)**	**1.15 (1.08, 1.22)**
Late chemotherapy			
Adjusted odds ratio (95% CI)*	Reference	**0.83 (0.70, 0.99)**	**0.70 (0.61, 0.82)**

*: All data are adjusted for patient demographics, clinical factors, and market factors, using 2-level hierarchical generalized linear models and clustering patients by hospital referral region. Bold indicates $p<0.05$.