Am J Transl Res 2021;13(11):13034-13042
www.ajtr.org /ISSN:1943-8141/AJTR0136751

Original Article

Insufficient pain control for patients with cancer and dementia during terminal cancer stages

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Received June 25, 2021; Accepted September 7, 2021; Epub November 15, 2021; Published November 30, 2021

Abstract: Purpose: To estimate differences in pain control between patients with cancer and with or without dementia during terminal cancer stages 3 months or 1 month before cancer death. Patients and methods: We conducted frequency matching cohort for age, sex, and year of death for both groups at a 1:4 ratio. The prescription prevalence, total cumulative dose, and average daily dose of opioids during the terminal cancer stages 3 months and 1 month before cancer death were estimated. Results: Patients with cancer and dementia were prescribed lower amounts of opioids 3 months before death (57.5% vs. 73.9%, respectively; adjusted odds ratio [OR] 0.46; 95% confidence interval [CI] 0.44-0.49) and 1 month before death (54.4% vs. 70.3%, respectively; adjusted OR 0.50; 95% CI 0.47-0.53). The total cumulative dose of opioids (mg) was lower in patients with cancer and dementia 3 and 1 month(s) before death (3 months: 1,578 mg vs. 2,666 mg, respectively; β=-1,125.9, *P*<0.001; 1 month: 921 mg vs. 1,533 mg, respectively; β=-622.1, *P*<0.001). The average daily opioid dose (mg/day), patients with cancer and dementia received a lower dose 3 months before death (31 mg vs. 48 mg; β=-22.6, *P*<0.001) and 1 month before death (38 mg vs. 60 mg; β=-17.1, *P*<0.001). Conclusion: The prevalence of opioid prescription was significantly lower in patients with both cancer and dementia during their terminal cancer stages 3 months and 1 month before death.

Keywords: Opioid, cancer, dementia, terminal stage, death

Introduction

Pain is often unrecognized and underestimated in older individuals [1], especially in patients diagnosed as having dementia or cognitive impairment [2]. Research has shown that older adults with dementia appear to receive less pain control than do older adults with normal cognitive ability, despite having diseases of similar severity [3-5]. This discrepancy may be attributed to the inability of older patients with dementia or early-onset dementia to accurately describe their pain [6]. Opioids are widely used for treatment of cancer-related pain because of their safety [7]. Although neuropathic pain is difficult to treat, a favorable response to opioid-based analgesia is often possible [8]. However, cancer pain assessment is a complex undertaking, especially in patients with dementia [9].

The prevalence of pain and pain management in patients with dementia has only recently been explored, although the prevalence of pain among this patient group is high (12%-76%) [10, 11]. Dementia is associated with a reduced quality of life [12], impaired physical function, sleep disturbance, and a risk of falls; furthermore, dementia may be linked to both neuropsychiatric symptoms and functional impairment. Opioid administration may be problemat-

ic in patients with dementia because of the consequent sedative side effects and their association with a reduction in cognitive functioning [6]. This has raised concerns among clinicians, who are consequently often reluctant to prescribe opioids for pain control [13]. However, pain is associated with and reduces quality of life as well as patient comfort, and this is a serious concern that should be addressed [14]. Additionally, pain treatment can improve behavioral symptoms in patients with dementia [15, 16]. Pain is experienced by most patients with cancer, and opioids are the mainstay treatment for cancer pain and may provide effective pain relief for most patients.

Pain assessment and treatment is likely lower in people with dementia in general and not limited to those with cancer; however, the prevalence of pain is generally high in patients with cancer. Until now, few studies have investigated the extent and differences of pain control during terminal cancer stages between patients with cancer who have and do not have dementia. By employing a vast amount of data from Taiwan's National Health Insurance Research Database (NHIRD), this study investigated sufficient and insufficient pain control during the terminal cancer stages of 3 months and 1 month prior to death between patients with cancer who have and do not have dementia.

Patients and methods

Data source

This retrospective cohort study used data derived from reimbursement claims in the Longitudinal Health Insurance Database for Catastrophic Illness Patients (LHID-CIP) from January 1, 2000, to December 31, 2012. The LHID-CIP is a part of the NHIRD that contains the comprehensive medical data of patients with cancer for clinical visits, including prescription details and diagnostic codes based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM). The National Health Insurance (NHI) program is Taiwan's universal health insurance system, which covers more than 99% of Taiwan's population of 24 million [17-26]. The NHIRD database contains information on the demographics of the insured population, diagnostic codes, care, and medications for inpatients and outpatients [17-26]. The National Health Research Institute (NHRI) manages the NHIRD and uses random identification numbers to ensure patient privacy. Data was anonymized throughout the study, and the requirement for written informed consent was waived [17-26]. The study was approved by the Institutional Review Board of Tzu Chi Medical Center (reference number: IRB103-51-C).

Study population

By using LHID-CIP files, we identified 549,827 patients with the 6 most common types of cancer in Taiwan, namely colorectal (ICD-9-CM codes 153 & 154), liver (ICD-9-CM code 155), lung (ICD-9-CM code 162), breast (ICD-9-CM code 174), oral (ICD-9-CM codes 140-141, 143-146, and 148-149), and prostate cancer (ICD-9-CM code 185). We excluded a total of 349,571 patients on the basis of the following criteria: (1) diagnosis of more than one cancer (*N*=37,230), (2) age <20 years (*N*=462), (3) still living (*N*=271,414), (4) traffic accident before death (*N*=6,463), (5) not an inpatient within 1 month of death (*N*=34,002), and (6) schizophrenia (*N*=1,417).

Of the remaining 200,256 patients, a total of 8,471 (4.26%) were had both cancer and dementia (cancer-dementia group) and 190,368 (95.74%) had cancer but no dementia (cancer-nondementia group). We used the following diagnostic criteria for dementia: (1) having a Catastrophic Illness Card for dementia, (2) diagnosed as having dementia by a psychiatrist or neurologist during a previous hospitalization, and (3) diagnosed as having dementia at least twice within in 1 year in outpatient services by a psychiatrist or neurologist. People who met all the aforementioned diagnostic criteria were considered to have dementia. People who met all the aforementioned diagnostic criteria were considered to have dementia. In the aforementioned definition of dementia, our enrolled cancer-dementia patients all have received neurological evaluation by a psychiatrist or neurologist and judged as moderate-severe stage dementia based on the Global Deterioration Scale [27] by a psychiatrist or neurologist, because the Catastrophic Illness Card in Taiwan for dementia was only granted for moderate to severe dementia patients with stage 5 dementia symptoms at least [27]. There are no patients with dementia at early phase only

affect memory but not cognition in our study. To obtain the final study sample for the nondementia group, we conducted frequency matching of patients with those of the dementia group according to age, sex, primary cancer type, and year of death at a 1:4 ratio. Our study population comprised 7,111 patients in the dementia group and 28,444 in the nondementia group through frequency matching.

Covariates

The Charlson Comorbidity Index (CCI) was calculated to represent each patient's overall comorbid status [28-33]. Dementia and mental impairment were excluded from the CCI scores to prevent repetitive adjustment in the multivariate analysis. Comorbidities were required to be diagnosed in at least one hospital admission or two outpatient services during the 1-year period before death, according to previous publications of the NHIRD [17-26].

Endpoint

We studied the difference in the prevalence of opioid prescription between patients with cancer and dementia and patients with cancer and no dementia at 3 months and 1 month before death. The accumulated dose and the average daily dosage (mg/day) of opioids at 3 and 1 month(s) before death were evaluated. Different opioids were converted to the equivalent dosage of morphine in oral form for comparison. The endpoint was the prescribed dose of opioids and their duration for patients with cancer and dementia and those with cancer and no dementia who died within 3 months. We estimated, through stratified analysis with multivariate analysis, the prescription and dosage of opioids for patients with different cancers with and without dementia during the terminal stages of 3 months and 1 month before death. Dementia caused by metastatic brain tumor were not excluded from our enrolled patients in cancer-dementia group, because the endpoint was the prescribed dose of opioids and their duration for patients with cancer and dementia and those with cancer and no dementia who died within 3 months, whatever the etiology of dementia. We also performed the stratified analysis of different subgroups as Alzheimer's dementia or non-Alzheimer's dementia, because previous study has already showed that cancer patients with severe Alzheimer's disease received less opioid [34].

Statistical analysis

An independent *t* test was used to analyze continuous variables, and a chi-squared test was used for categorical variables. Multiple logistic regression and multiple linear regression were performed with adjustment for all characteristics listed in **Table 1**, including age, sex, primary cancer type, CCI, year of death, and time between cancer diagnosis and death. Adjusted odds ratios (OR) were calculated with a 95% confidence interval (CI). A *P* value of <0.05 was considered statistically significant. All statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

In total, 7,111 patients were included in the cancer-dementia group and 28,444 were included in the cancer-nondementia group. Variables such as age, gender, and type of primary cancer were similar between the two groups of patients, but the CCI varied slightly between the groups. Although dementia was removed from the CCIs, other comorbidities in the remaining CCI were more prevalent in the cancer-dementia group compared with the cancer-nondementia group (**Table 1**).

Patients with cancer and dementia were prescribed a lower amount of opioids compared with those with cancer and no dementia 3 months before death (57.5% vs. 73.9%, respectively; adjusted OR 0.46; 95% CI 0.44-0.49) and of 1 month before death (54.4% vs. 70.3%, respectively; adjusted OR 0.50; 95% CI 0.47-0.53, *P*<0.001; **Table 2**). The total accumulated opioid dose (mg) was lower in patients with cancer and dementia compared with patients with cancer and no dementia at 3 and 1 month(s) before death (3 months: 1,578 mg vs. 2,666 mg, respectively; β=-1,125.9, *P*<0.001; 1 month: 921 mg vs. 1,533 mg, respectively; β=-622.1, *P*<0.001). We also estimated the average daily dose (mg/day) of opioids for patients with cancer and dementia, and they received a lower average daily dose than did those with cancer and no dementia 3 months before death (31 mg vs. 48 mg; β=-22.6, *P*<0.001) and 1 month before death (38 mg vs. 60 mg; β=-17.1, *P*<0.001). Whatever

Table 1. Demographic characteristics of patients with cancer and dementia and patients with cancer and no dementia during terminal cancer stages

	All patients with cancer				*P* value
	Cancer-Dementia (*N*=7,111)		Cancer-Nondementia (*N*=28,444)		
	N	%	*N*	%	
Type of cancer					1.000*
Oral cancer	301	4.2	1,204	4.2	
Colorectal cancer	1,942	27.3	7,768	27.3	
Liver cancer	1,602	22.5	6,408	22.5	
Lung cancer	1,948	27.4	7,792	27.4	
Breast cancer	300	4.2	1,200	4.2	
Prostate cancer	1,018	14.3	4,072	14.3	
Age at death (years)					1.000*
<75	1,372	19.3	5,488	19.3	
75-79	1,507	21.2	6,028	21.2	
80-84	2,003	28.2	8,012	28.2	
≥85	2,229	31.4	8,916	31.4	
Sex					1.000*
Male	4,521	63.6	18,084	63.6	
Female	2,590	36.4	10,360	36.4	
Charlson Comorbidity Index score					<0.001*
0-2	659	18.4	5,244	9.3	
3-4	2,623	42.2	11,999	36.9	
5-6	2,022	17.2	4,900	28.4	
7-8	872	9.8	2,798	12.3	
≥9	935	12.3	3,503	13.2	

**P* values were determined with a Chi-squared test.

Table 2. Multivariate analysis of opioid prescription between patients with cancer and dementia and patients with cancer and no dementia 3 months and 1 month before death

	1 month before death			3 months before death		
	Dementia (*N*=7,111)	No dementia (*N*=28,444)	*P* Value	Dementia (*N*=6,015)	No dementia (*N*=24,060)	*P* Value
Prescription of opioids*			<0.001			<0.001
N (%)	3,865 (54.4%)	19,992 (70.3%)		3,460 (57.5%)	17,770 (73.9%)	
Adjusted OR (95% CI)	0.50 (0.47-0.53)	Referent		0.46 (0.44-0.49)	Referent	
Total accumulated dose (mg)†			<0.001			<0.001
Mean ± SD	921±2,243	1,533±3,908		1,578±4,209	2,666±7,085	
β ± SE	-622.1±48.0	Referent		-1,125.9±94.8	Referent	
Average daily dose (mg/day)†			<0.001			<0.001
Mean ± SD	38±81	60±129		31±63	48±93	
β ± SE	-22.6±1.6	Referent		-17.1±1.3	Referent	

*Multiple logistic regression, adjusted for age, sex, primary malignancy, Charlson Comorbidity Index, and year of death. †Multiple linear regression, adjusted for age, sex, primary malignancy, Charlson Comorbidity Index, and year of death. β, beta coefficient; OR, odds ratio; SD, standard deviation; SE, standard error.

Alzheimer's dementia or non-Alzheimer's dementia, the prevalence of opioid prescription was significantly lower in patients with both cancer and dementia during their terminal cancer stages 3 months and 1 month before death (Supplementary Table 1).

Opioid prescriptions and dosages for patients with different cancers with or without dementia 3 months and 1 month before death were also estimated using stratified analysis (**Table 3**). In the stratified analysis of different cancer types, the prescription, total accumulated dose, and

Table 3. Prescription and dosage of opioids for patients with different cancer types with or without dementia 3 months and 1 month before death

Diagnosis of dementia	Oral cancer		Colorectal cancer		Liver cancer		Lung cancer		Breast cancer		Prostate cancer	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
3 months before death												
Number	255	1,020	1,689	6,756	1,276	5,104	1,531	6,124	283	1,132	981	3,924
Use of opioids												
%	65.9	82.5	49.8	70.5	64.3	77.6	68.4	79.5	51.6	67.3	44.7	65.6
P value*	<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
Total accumulated dose (mg)												
Mean	2820	5834	1216	2455	1387	1924	2213	3209	1668	2492	1108	2373
P value†	<0.001		<0.001		<0.001		<0.001		0.029		<0.001	
Average daily dose (mg/day)												
Mean	44	82	26	46	30	40	42	56	31	45	20	41
P value†	<0.001		<0.001		<0.001		<0.001		0.005		<0.001	
1 month before death												
Number	301	1,204	1,942	7,768	1,602	6,408	1,948	7,792	300	1,200	1,018	4,072
Prescription of opioids												
%	62.1	76.9	47.7	66.2	59.4	74.2	65.3	76.6	47.0	62.3	38.2	60.4
P value*	<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
Total accumulated dose (mg)												
Mean	1471	2976	737	1470	855	1127	1276	1785	727	1708	595	1332
P value†	<0.001		<0.001		<0.001		<0.001		0.001		<0.001	
Average daily dose (mg/day)												
Mean	55	102	31	58	36	49	52	68	32	65	24	52
P value†	<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	

*Multiple logistic regression, adjusted for age, sex, primary malignancy, Charlson Comorbidity Index, and year of death. †Multiple linear regression, adjusted for age, sex, primary malignancy, Charlson Comorbidity Index, and year of death.

average daily dose of opioids were significantly lower for patients with cancer and dementia compared with patients with cancer and no dementia at both 3 months and 1 month prior to death. Moreover, we observed an increase in the average opioid dose administered per day from 3 to 1 month(s) before death for all patients with cancer, regardless of dementia status.

Discussion

Patients with dementia are a vulnerable group in which pain is frequently unrecognized, underestimated, and undertreated [35-37]. Dementia prevents medical personnel from detecting pain in patients and obscures the self-reporting of pain by patients, further exacerbating its undertreatment [38]. In a study by Reynolds et al., cognitive impairment was strongly associated with fewer reports of pain and less treatment of pain overall. Moreover, the researchers reported a lower prevalence of pain medication use in patients with severe cognitive impairment [39], even though effective pain management can improve patients' quality of life. Pain control is also critical for patients diagnosed as having cancer and dementia, and other studies have confirmed that pain medication is underadministered in patients with dementia [35-37]. Pain control is vital for patients with terminal-stage cancer and is associated with higher quality of life in hospice care [40]. According to literature review, no study has yet estimated sufficient or insufficient pain control in patients with cancer and dementia. Therefore, we examined the differences in pain control between patients with cancer and dementia and those with cancer and no dementia during the terminal stages of 3 months and 1 month before death.

Table 1 indicates that most covariates except CCI were balanced in our study. The CCIs were higher in patients with cancer and dementia than in patients with cancer and no dementia. Additional comorbidities have no effect on opioid prescription (primary endpoint in our study) in patients with terminal-stage cancer [41]. Therefore, the imbalanced CCI scores likely did

not bias our hypothesis. We found no evidence that comorbidities interfered with opioid prescription in patients with cancer during the 3 months and 1 month before death. We used multiple logistic regressions and multiple linear regression, adjusted for age, sex, primary malignancy, CCIs, and year of death, to account for this unexpected bias in relation to comorbidities and opioid prescription.

To date, the following self-reported and observational pain assessment tools for patients with dementia are available: the Wong-Baker Faces pain scale, the Pain Assessment in Advanced Dementia scale, and the Doloplus-2 pain scale [42]. However, self-reported pain and the aforementioned observational tools have variable correlations [42]. Nursing practices of pain management for older patients with dementia also varies [6]. No specific guidelines for the objective evaluation of pain have been established, making its assessment difficult [43]. This can prove especially problematic for patients with impaired cognition because behavioral indicators cannot be reliably used to evaluate pain in this population [44]. Such patients cannot describe or vocalize their pain, and specific tools for evaluating pain in people with moderate to severe dementia have only recently been developed [34]. The consequent lower dosage of analgesics administered to patients with cognitive impairment may thus account for the lower reported prevalence of pain in patients with dementia. This is a serious issue for a particularly vulnerable population living with terminal-stage cancer. The quality of life of patients with cancer and dementia is poor because of the severe pain they may be in, and they may experience severe cancer pain until death. This pressing clinical issue requires discussion for the sake of this disadvantaged group. Thus, we intended to call attention to the fact that patients with cancer and dementia receive insufficient pain control during the terminal stages of the disease (**Tables 2** and **3**), at 3 months and 1 month before death. **Tables 2** and **3** present the low prevalence of prescription, low total accumulated dose, and low average daily dose of opioids in patients with cancer and dementia during the terminal stages compared with patients with cancer and no dementia. Our study showed the potentially severe pain that this disadvantaged population may experience. The development of an assessment tool to evaluate pain levels in patients with cancer and dementia is necessary, as is sufficient pain control for these patients during terminal cancer stages.

In Taiwanese and Asian society, opioids such as morphine are labeled as addictive drugs that have the potential to harm patients' bodies and shorten their lifespans [45]. Although the majority of patients agree with and accept opioid administration as a mainstream pain treatment, some patients or families reject their usage for pain control [46, 47]. Different political and cultural attitudes toward treatment with opioids may impact the undertreatment of pain in patients with cancer and dementia because we have no useful and fast assessment to accurately assess their pain levels [48]. The underadministration of opioids seldom occurs in palliative or hospice wards, but it is seen in other facilities. As observed by Sykes et al., no evidence has indicated that the initiation of pain treatment or increased dosage of opioids or sedatives is associated with death [41]. As a result, we must ensure that patients with cancer and dementia in terminal stages are not underprescribed opioid pain treatment regardless of cancer type (**Tables 2** and **3**). Without this caution, patients with cancer and dementia may experience severe pain in their terminal days. Because the previous study has already showed that cancer patients with severe Alzheimer's disease received less opioid [34], we also stratified subgroup analysis of Alzheimer's dementia or non-Alzheimer's dementia in the Supplementary Table 1. Whatever Alzheimer's dementia or non-Alzheimer's dementia, the prevalence of opioid prescription was significantly lower in patients with both cancer and dementia during their terminal cancer stages 3 months and 1 month before death.

The strength of our study is that it is the first and the largest study to estimate the prevalence of opioid prescription in terminal cancer stages, comparing patients with cancer and dementia to those with cancer and no dementia. Our study is also the first to undertake stratified analysis of cancer types in these patients in these terminal cancer stages, and it revealed a lower prevalence of opioid prescription in patients with cancer and dementia (**Tables 2** and **3**). By using the NHIRD database, we were

able to tabulate the average daily opioid dosage among patients with cancer and with or without dementia and identify differences in these metrics among cancer types. The present study bolsters evidence on the reportedly low prevalence of opioid prescription and administration of morphine in patients with dementia relative to other people with similar sociodemographic and clinical characteristics (**Table 1**). Our findings therefore underscore the need for clinicians to pay careful attention to the pain control of cancer patients with dementia to ensure adequate treatment. The combined use of multiple assessment tools should be considered in the future.

Our study had some limitations. First, pain is evaluated using specific tools, but these tools are insufficient for meeting the challenges of diagnosing pain in patients with cancer and dementia. Therefore, we have no details on the pain levels of this patient group, and this lack of information in the database limits our study. Nevertheless, our results reflect the willingness levels of doctors to prescribe opioids to patients with cancer and dementia who are experiencing pain. Our study provides clinicians with valuable data concerning the undertreatment of pain in these patients. Second, the database did not contain data on dementia severity, which is particularly relevant because the vocalization of pain or discomfort may not yet be compromised in the early stages of dementia. Although we used stringent criteria to identify dementia to prevent its overdiagnosis, we were unable to assess dementia severity. The inclusion of patients with early-stage dementia might therefore have overestimated the prevalence of opioid prescription in the dementia group. Third, the NHIRD contains no information regarding dietary habits, socioeconomic status, or body mass index, all of which might be confounding factors for opioid use. However, considering the magnitude and statistical significance of the effects observed in this study, these limitations are unlikely to have affected the conclusions.

Conclusions

The prevalence of opioid prescription is significantly low in patients with cancer and dementia compared with patients with cancer but no dementia in the terminal cancer stages of 3 months or 1 month before death, regardless of cancer type. Patients with cancer and dementia may experience severe pain in terminal-stage cancer. Rapid and useful assessment tools to measure pain levels in these patients are necessary and will lead to more adequate pain control.

Acknowledgements

Lo-Hsu Medical Foundation, LotungPoh-Ai Hospital, supports Szu-Yuan Wu's work (Funding Number: 110908, 10909, 11001, 11002, 11003, 11006, and 11013).

Disclosure of conflict of interest

None.

Abbreviations

OR, odds ratio; CI, confidence interval; LHID-CIP, Longitudinal Health Insurance Database for Catastrophic Illness Patients; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; NHI, National Health Insurance; NHIRD, National Health Insurance Research Database; NHRI, National Health Research Institute; CCI, Charlson Comorbidity Index.

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Supplementary Table 1. Subgroup analysis of opioid prescription between patients with cancer and Alzheimer's dementia or non-Alzheimer's dementia and patients with cancer and no dementia 3 months and 1 month before death

	1 month before death			3 months before death		
	Alzheimer's Dementia (*N*=4,622)	Non-Alzheimer's Dementia (*N*=2,489)	No dementia (Ref.) (*N*=28,444)	Alzheimer's Dementia (*N*=3,970)	Non-Alzheimer's Dementia (N=2,045)	No dementia (Ref.) (*N*=24,060)
Prescription of opioids*						
N (%)	2,311 (50.0%)	1,554 (62.4%)	19,992 (70.3%)	2,070 (52.1%)	1,390 (68.0%)	17,770 (73.9%)
Adjusted OR (95% CI)	0.45 (0.39-0.47)	0.55 (0.51-0.58)	Referent	0.44 (0.42-0.47)	0.55 (0.52-0.59)	Referent
P Value	<0.001	<0.001		<0.001	<0.001	
Total accumulated dose (mg)†						
Mean ± SD	865±2,142	976±2,377	1,533±3,908	1,499±3,999	1,672±4,553	2,666±7,085
β ± SE	-594.1±47.0	-640.7±50.8	Referent	-1,068.8±90.1	-1,192.5±98.6	Referent
P Value	<0.001	<0.001		<0.001	<0.001	
Average daily dose (mg/day)†						
Mean ± SD	36±77	40±85	60±129	29±60	33±67	48±93
β ± SE	-21.5±1.5	-23.3±1.7	Referent	-16.3±1.2	-18.2±1.4	Referent
P Value	<0.001	<0.001		<0.001	<0.001	

*Multiple logistic regression, adjusted for age, sex, primary malignancy, Charlson Comorbidity Index, and year of death. †Multiple linear regression, adjusted for age, sex, primary malignancy, Charlson Comorbidity Index, and year of death. β, beta coefficient; OR, odds ratio; SD, standard deviation; SE, standard error; Ref., reference group.