



# Association of Zolpidem With Increased Mortality in Patients With Brain Cancer: A Retrospective Cohort Study Based on the National Health Insurance Service Database

Sungeun Hwang<sup>a,b,c</sup>

Hyoshin Son<sup>a,b,d</sup>

Manho Kim<sup>a,b,e</sup>

Sang Kun Lee<sup>a,b</sup>

Ki-Young Jung<sup>a,b,f,g</sup>

<sup>a</sup>Department of Neurology,  
Seoul National University Hospital,  
Seoul, Korea

<sup>b</sup>Department of Translational Medicine,  
Seoul National University  
College of Medicine, Seoul, Korea

<sup>c</sup>Department of Neurology,  
Ewha Womans University  
Mokdong Hospital, Seoul, Korea

<sup>d</sup>Department of Neurosurgery,  
Seoul National University Hospital,  
Seoul, Korea

<sup>e</sup>Neuroscience and Protein  
Metabolism Research Center,  
Seoul National University  
College of Medicine, Seoul, Korea

<sup>f</sup>Neuroscience Research Institute,  
Seoul National University  
College of Medicine, Seoul, Korea

<sup>g</sup>Sensory Organ Research Institute,  
Medical Research Center,  
Seoul National University  
College of Medicine, Seoul, Korea

**Background and Purpose** Zolpidem is one of the most common hypnotics prescribed to treat insomnia worldwide. However, there are numerous reports of a positive association between zolpidem and mortality, including an association with increased cancer-specific mortality found in a Taiwanese cohort study. This study aimed to determine the association between zolpidem use and brain-cancer-specific mortality in patients with brain cancer.

**Methods** This population-based, retrospective cohort study analyzed data in the National Health Insurance Service database. All incident cases of brain cancer at an age of  $\geq 18$  years at the time of brain cancer diagnosis over a 15-year period (2003–2017) were included. A multivariate Cox regression analysis after adjustment for covariables was performed to evaluate the associations of zolpidem exposure with brain-cancer-specific and all-cause mortality.

**Results** This study identified 38,037 incident cases of brain cancer, among whom 11,823 (31.1%) patients were exposed to zolpidem. In the multivariate Cox regression model, the brain-cancer-specific mortality rate was significantly higher in patients who were prescribed zolpidem than in those with no zolpidem prescription (adjusted hazard ratio [HR]=1.14, 95% confidence interval [CI]=1.08–1.21,  $p < 0.001$ ). Zolpidem exposure was significantly associated with increased brain-cancer-specific mortality after adjustment in younger adults (age 18–64 years; adjusted HR=1.37, 95% CI=1.27–1.49) but not in older adults (age  $\geq 65$  years; adjusted HR=0.94, 95% CI=0.86–1.02).

**Conclusions** Zolpidem exposure was significantly associated with increased brain-cancer-specific mortality in patients with brain cancer aged 18–64 years. Further prospective studies are warranted to understand the mechanism underlying the effect of zolpidem on mortality in patients with brain cancer.

**Keywords** brain cancer; zolpidem; mortality.

**Received** May 14, 2021

**Revised** August 7, 2021

**Accepted** August 9, 2021

## Correspondence

Ki-Young Jung, MD, PhD  
Department of Neurology,  
Seoul National University Hospital,  
101 Daehak-ro, Jongno-gu,  
Seoul 03080, Korea

**Tel** +82-2-2072-4988

**Fax** +82-2-2072-2474

**E-mail** jungky@snu.ac.kr

## INTRODUCTION

Hypnotics are commonly used for treating sleep disorders, but adverse effects from unnecessary sedative-hypnotics use are widely reported. Common adverse effects of hypnotics include cognitive impairment, fatigue, traffic collisions, falls, infections, and even cancer development.<sup>1</sup> Furthermore, significantly increased mortality is associated with the use of sedative-hypnotics.<sup>1–5</sup> The imidazopyridine derivative zolpidem is one of the most common hypnotics prescribed to treat insomnia worldwide. In the USA, 1.08% of community-dwelling adults were prescribed zolpidem 1999–2010, and more than 23 million zolpidem pills were prescribed in 2005. In Taiwan, zolpidem was the most common Z-drug prescribed to older adults (86.7% in 2010).<sup>6</sup> A retrospective survey from a tertiary hospital in South Korea

© This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

revealed that zolpidem was prescribed to 8.7% of all older outpatients.<sup>7</sup>

The association between zolpidem and mortality has been investigated by many researchers. A matched-cohort study from Pennsylvania, USA found that zolpidem was associated with increased mortality in a dose-dependent manner.<sup>1</sup> A Taiwanese cohort study found that the cancer-specific mortality rate was higher in patients with zolpidem exposure (adjusted hazard ratio [HR]=1.65, 95% confidence interval [CI]=1.57–1.74), although zolpidem exposure was associated with a lower risk of overall mortality (adjusted HR=0.73, 95% CI=0.71–0.75).<sup>8</sup>

Among the numerous types of cancers, patients with brain cancer may be particularly vulnerable to sleep disorders because circadian oscillators and sleep-wake-promoting centers that regulate the sleep-wake cycle reside in the brain. A thorough review of studies on sleep disturbances among patients with brain cancer found that the reported prevalence of sleep disturbances ranged from 17% to 54%.<sup>9</sup> Another systematic review found that 27%–34% of patients with brain cancer complained of moderate-to-severe sleep disturbances.<sup>10</sup> Furthermore, insomnia was significantly related to disease progression in a prospective study that included patients with high-grade glioma.<sup>11</sup> While the impact of hypnotics on cognitive function and sleep quality for patients with brain cancer has been evaluated previously,<sup>12</sup> to the best of our knowledge no study has investigated the association between hypnotics and mortality in patients with brain cancer.

We hypothesized that zolpidem is associated with increased brain-cancer-specific mortality. We investigated the association between zolpidem and mortality in patients with brain cancer by performing a population-based, retrospective cohort study utilizing the database of the National Health Insurance Service (NHIS) of the Republic of Korea. The NHIS database provides nationwide, population-based information on all medical services and medications.<sup>13</sup> Linked to the national mortality data, the NHIS database also provides reliable data regarding deaths with a long follow-up period, and so this database can be used as a data source for a retrospective cohort study.

## METHODS

### Data source and study population

International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes were utilized to identify the diagnosis of each patient. The cause of death for each individual was obtained from Statistics Korea (KOSTAT) for patients who died during the study inclusion period.<sup>14</sup>

The study population comprised adults (age  $\geq 18$  years) who were diagnosed with malignant neoplasm of the cerebral meninges (ICD-10 code: C70.0) or brain (ICD-10 code: C71) between January 2003 and December 2017. Patients with a diagnosis of malignant neoplasms of the cerebral meninges or brain in 2002 were excluded so as to only include incident cases between 2003 and 2017. Patients diagnosed with malignant neoplasms originating from outside the central nervous system (ICD-10 codes: C00–C69, C70.1–C70.9, and C72–C97) between 2002 and 2017 were excluded in order to minimize the potential influence of other cancers on survival.

The Institutional Review Board of Seoul National University Hospital approved this study (E-2006-005-1129) and waived the requirement to obtain informed consent since only deidentified data were used.

### Variables

The onset of brain cancer was defined as the first day with an ICD-10 code for brain cancer (C70.0 and C71.0–C71.9). Data on the age at a brain cancer diagnosis and sex were obtained. The cause of death for every death that occurred during the study period in the KOSTAT database was reviewed to determine whether the patient died from brain cancer. The survival duration was defined as the number of days between a brain cancer diagnosis and death.

Data on comorbid diseases and prescribed medications were also obtained from the NHIS database. Patients with a diagnosis of nonorganic sleep disorders (ICD-10 code: F51.x) or organic sleep disorders (ICD-10 code: G47.x) were classified as exhibiting sleep disorders. Furthermore, patients with a diagnosis of depressive episode (ICD-10 code: F32.x) or recurrent depressive disorder (ICD-10 code: F33.x) were considered to exhibit depression. Zolpidem exposure was defined as the prescription of any form of zolpidem (regular and controlled-release forms). Exposure to any of the following antidepressants available in South Korea was identified: amitriptyline, amoxapine, clomipramine, fluoxetine, fluvoxamine, imipramine, mirtazapine, moclobemide, nortriptyline, paroxetine, sertraline, tianeptine, trazodone, venlafaxine, milnacipran, bupropion, citalopram, escitalopram, tandospirone, duloxetine, desvenlafaxine, or vortioxetine.

### Statistical analysis

The characteristics of the study population were compared between the zolpidem exposure and no-exposure groups using the *t*-test for continuous variables and the chi-square test for categorical variables. The mortality risk for zolpidem exposure was analyzed using the Cox regression model in a multivariate analysis to calculate the HR and 95% CI after adjusting for the possible confounding factors of age at a brain cancer

diagnosis, sex, sleep disorder, depression, and antidepressants. Patients were divided into two groups for further analysis according to the age at the brain cancer diagnosis: younger adults (18–64 years old) and older adults ( $\geq 65$  years old). The HR for each group was computed. With respect to the primary analysis, deaths attributable to brain cancer were used in a survival analysis. Deaths due to causes other than brain cancer were considered censored data, as were patients who were alive at the end of the study period (December 31, 2017). The cause of death determined from KOSTAT was based mainly on death certificates. Considering possible errors in death certificates, a secondary analysis evaluating the risk of all-cause mortality from zolpidem was performed. Statistical analysis was performed using R software (R Core Team, 2019, R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; <https://www.r-project.org/>).

## RESULTS

We identified 38,037 incident cases of brain cancer in adults between 2003 and 2017 (Fig. 1): 16,791 (44.1%) males and 21,246 (55.9%) females. The age at the brain cancer diagnosis was  $53.3 \pm 17.9$  years (mean  $\pm$  standard deviation), and 17,714 (46.6%) participants were diagnosed with sleep disorders, 11,823 (31.1%) were exposed to zolpidem, 16,030 (42.1%) were diagnosed with depression, and 18,573 (48.8%) were exposed to at least one antidepressant. The overall survival time was  $6.8 \pm 5.3$  years. Overall 14,521 (38.2%) patients died during the follow-up period, of which 8,839 (23.2%) died from brain cancer.

### Comparison of characteristics according to exposure to zolpidem

Zolpidem exposure occurred in 11,823 (31.1%) patients between 2003 and 2017 (Table 1). Compared with the no-exposure group, the exposure group was older at the brain cancer diagnosis (57.1 years vs. 51.6 years,  $p < 0.001$ ) and had higher rates of all-cause mortality (41.4% vs. 36.7%,  $p < 0.001$ ) and brain-cancer-specific mortality (23.9% vs. 22.9%,  $p = 0.038$ ). Sleep disorders (91.8% vs. 26.2%,  $p < 0.001$ ), depression (63.4% vs. 32.6%,  $p < 0.001$ ), and antidepressant use (69.8% vs. 39.4%,  $p < 0.001$ ) were more prevalent in the exposure group than in the no-exposure group.

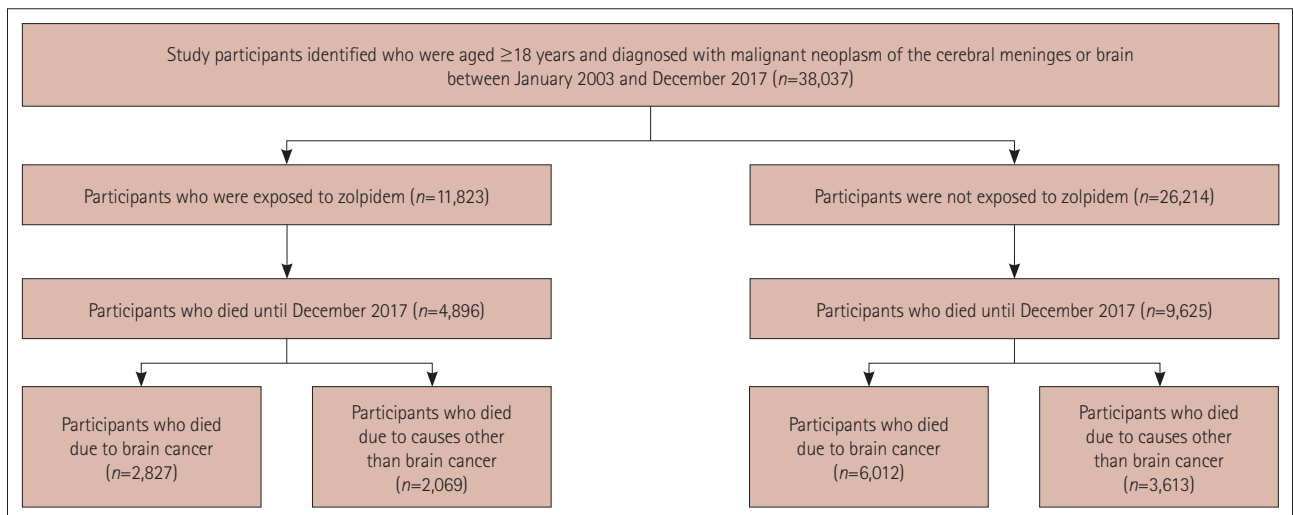
### Mortality risk of zolpidem on brain-cancer-specific mortality

Table 2 lists the HRs of the covariables of brain-cancer-specific mortality

**Table 1.** Characteristics of the study population according to exposure to zolpidem

Variables	Exposure (n=11,823, 31.1%)	No exposure (n=26,214, 68.9%)	p
Age at brain cancer diagnosis (yr)	57.1 $\pm$ 16.4	51.6 $\pm$ 18.3	<0.001
Sex			<0.001
Male	4,468 (37.8)	12,323 (47.0)	
Female	7,355 (62.2)	13,891 (53.0)	
Sleep disorder	10,855 (91.8)	6,859 (26.2)	<0.001
Depression	7,496 (63.4)	8,534 (32.6)	<0.001
Antidepressant use	8,250 (69.8)	10,323 (39.4)	<0.001
Overall deaths	4,896 (41.4)	9,625 (36.7)	<0.001
Brain-cancer-specific mortality	2,827 (23.9)	6,012 (22.9)	0.038

Data are mean  $\pm$  standard deviation or n (%) values.



**Fig. 1.** Flow diagram of the study. We identified 38,037 participants aged  $\geq 18$  years and diagnosed with malignant neoplasm of the cerebral meninges or brain between January 2003 and December 2017. The 11,823 participants who were exposed to zolpidem included 4,896 who died up to the end of the study period, while 9,625 of the 26,214 participants who were not exposed to zolpidem died up to the end of the study period.

cific mortality. Increased brain-cancer-specific mortality was associated with male sex (unadjusted HR=1.50) and age at the brain cancer diagnosis (unadjusted HR=1.04). Diagnoses of sleep disorder (unadjusted HR=0.92), depression (unadjusted HR=0.83), and antidepressant use (unadjusted HR=0.71) were associated with decreased brain-cancer-specific mortality. Zolpidem use was not significantly associated with brain-cancer-specific mortality in the univariate analysis.

Zolpidem exposure was associated with increased brain-cancer-specific mortality before and after adjustment for age, sex, history of sleep disorder, depression, and antidepressant use in younger adults (18–64 years old, adjusted HR=1.37,  $p<0.001$ ) (Table 3). In older adults (age  $\geq 65$  years), zolpidem exposure seemed to be associated with decreased brain-cancer-specific mortality in the univariate analysis, but no significant association was observed in the multivariate analysis (adjusted HR=0.94,  $p=0.131$ ). Among younger adults, a

significant increase in brain-cancer-specific mortality was observed independent of sex (adjusted HR for younger males=1.41,  $p<0.001$ ; adjusted HR for younger females=1.32,  $p<0.001$ ). On the other hand, among older adults, brain-cancer-specific mortality was not associated with an increased risk of brain-cancer-specific mortality regardless of sex.

**Mortality risk of zolpidem for all-cause mortality**

Zolpidem exposure was associated with increased all-cause mortality in all adults (age  $\geq 18$  years) after adjustment for age, sex, history of sleep disorder, depression, and antidepressant use (adjusted HR=1.10,  $p<0.001$ ) (Table 4). As in the case of brain-cancer-specific mortality, the all-cause mortality risk was significantly higher in younger adults (age 18–64 years; adjusted HR=1.35,  $p<0.001$ ); however, no significant association between zolpidem and all-cause mortality was observed in older adults (age  $\geq 65$  years; adjusted HR=0.95,  $p=0.11$ ).

**Table 2.** HRs of brain-cancer-specific mortality for all variables

Variables	Value (n=38,037)	Brain-cancer-specific mortality (n=8,839)	Unadjusted HR (95% CI)	p
Age at brain cancer diagnosis (yr)	53.33±17.88	-	1.04 (1.03–1.04)	<0.001
Sex				<0.001
Male	16,791 (44.1)	4,671 (52.9)	1.50 (1.44–1.56)	
Female	21,246 (55.9)	4,168 (47.2)	1.00 (reference)	
Sleep disorder	17,714 (46.6)	3,995 (45.2)	0.92 (0.88–0.95)	<0.001
Zolpidem use	11,823 (31.1)	2,827 (32.0)	1.01 (0.97–1.06)	0.564
Depression	16,030 (42.1)	3,456 (39.1)	0.83 (0.79–0.86)	<0.001
Antidepressant use	18,573 (48.8)	3,721 (42.1)	0.71 (0.68–0.74)	<0.001

Data are n (%) or mean±standard deviation values, except where indicated otherwise. CI, confidence interval; HR, hazard ratio.

**Table 3.** HRs of brain-cancer-specific mortality for zolpidem exposure according to age groups

Age groups	Zolpidem use	Brain-cancer-specific mortality	Univariate analysis		Multivariate analysis	
			Unadjusted HR (95% CI)	p	Adjusted HR* (95% CI)	p
All adults ( $\geq 18$ yr, n=38,037)	11,823 (31.1)	8,839 (23.2)	1.01 (0.97–1.06)	0.564	1.14 (1.08–1.21)	<0.001
Younger adults (18–64 yr, n=26,563)	7,548 (28.4)	4,900 (18.4)	1.17 (1.11–1.25)	<0.001	1.37 (1.27–1.49)	<0.001
Older adults ( $\geq 65$ yr, n=11,474)	4,275 (37.3)	3,939 (34.3)	0.67 (0.63–0.72)	<0.001	0.94 (0.86–1.02)	0.131

Data are n (%) values, except where indicated otherwise. \*Adjusted for age, sex, history of sleep disorder, depression, and antidepressant use. CI, confidence interval; HR, hazard ratio.

**Table 4.** HRs of all-cause mortality for zolpidem exposure according to age groups

Age groups	All-cause mortality	Univariate analysis		Multivariate analysis	
		Unadjusted HR (95% CI)	p	Adjusted HR* (95% CI)	p
All adults ( $\geq 18$ yr, n=38,037)	14,521 (38.2)	1.10 (1.06–1.14)	<0.001	1.10 (1.05–1.15)	<0.001
Younger adults (18–64 yr, n=26,563)	6,724 (25.3)	1.22 (1.16–1.28)	<0.001	1.35 (1.26–1.44)	<0.001
Older adults ( $\geq 65$ yr, n=11,474)	7,797 (68.0)	0.73 (0.69–0.76)	<0.001	0.95 (0.90–1.01)	0.11

Data are n (%) values, except where indicated otherwise. \*Adjusted for age, sex, history of sleep disorder, depression, and antidepressant use. CI, confidence interval; HR, hazard ratio.

## DISCUSSION

This study identified 38,037 incident cases of brain cancer over a 15-year period in the NHIS database, which is a nationwide, comprehensive database that includes data on prescriptions, diagnoses, and demographics.

In our study population, 31.1% of patients with brain cancer were prescribed zolpidem. This is a much higher rate than those found in community-dwelling adults in the USA (1.08%)<sup>15</sup> and in older outpatients in South Korea (8.7%).<sup>7</sup> Frequent zolpidem prescription in patients with brain cancer is probably associated with high prevalence rates of sleep disorders and depression.

Zolpidem exposure was associated with brain-cancer-specific mortality before and after adjustment for confounders in younger adults (18–64 years old). The mortality risk of zolpidem is well established, and several underlying mechanisms have been reported. There are numerous reports of increased risks of traffic collisions and hip fractures due to falls in patients using zolpidem. Being prescribed zolpidem on the previous day was associated with an increased risk of a fatal motor vehicle collision (odds ratio=1.48, 95% CI=1.06–2.07).<sup>16</sup> The risk was further increased in patients with a high Charlson Comorbidity Index, younger patients, and new zolpidem users.<sup>16</sup> A significant association between Z-drugs and increased risk of hip fracture has also been observed (relative risk=1.90, 95% CI=1.68–2.13).<sup>17</sup> These results may account for the all-cause mortality rate being higher in zolpidem users, but they cannot explain their increased risk of brain-cancer-specific mortality.

A carcinogenic effect of zolpidem has been found in both human and animal models. According to FDA registration data, zolpidem and other hypnotics were associated with renal liposarcoma and renal lipoma in a rat model.<sup>18</sup> Although this result is insufficient to prove the carcinogenicity of zolpidem in humans, recent studies have provided evidence for this. A matched-cohort study found that zolpidem was associated with increased cancer incidence,<sup>1</sup> while a Taiwanese retrospective cohort study based on claim data revealed an increased risk of subsequent cancer among patients taking zolpidem.<sup>19</sup> The biological mechanism of zolpidem carcinogenicity has not been documented, but other hypnotics such as zopiclone, zaleplon, and ramelteon have shown clastogenicity.<sup>20</sup> Clastogens induce the disruption or breakage of chromosomes that results in mutagenesis, with cumulative mutations possibly leading to cancer initiation. Considering the carcinogenicity of zolpidem found in human epidemiological studies combined with clastogenicity in other hypnotics, it is plausible that zolpidem could contribute to cancer initiation and/or progression. Although there is still a lack of bio-

logical evidence, our study provides epidemiological evidence of increased brain-cancer-specific mortality in zolpidem users. More experimental studies aimed at acquiring evidence supporting our hypothesis are warranted in the future.

This study observed no significant association between the history of zolpidem use and mortality in older patients (age  $\geq 65$  years). A similar result was found in a 12-year prospective study of patients aged  $\geq 65$  years, in which benzodiazepines (adjusted HR=1.11, 95% CI=0.94–1.30) and Z-drugs including zolpidem (adjusted HR=0.92, 95% CI=0.71–1.20) were not associated with increased mortality after adjusting for confounding factors.<sup>21</sup> A higher prevalence of comorbidities and shorter life expectancy in older adults might explain the minimal effect of zolpidem on mortality in this population. In our study both the brain-cancer-specific mortality rate (37.3% vs. 28.4%,  $p < 0.001$ ) and the all-cause mortality rate (68.0% vs. 25.3%,  $p < 0.001$ ) were significantly higher in older adults. The survival duration was  $3.8 \pm 4.4$  years in older adults and  $8.1 \pm 5.2$  years in younger adults.

The brain-cancer-specific mortality rate was higher only in males among all adults, whereas it was associated with both males and females among younger adults. This sex discrepancy in older adults may explain the indistinctive effect of zolpidem in that population. The younger adults comprised 47.7% males and 52.3% females, whereas the older adults comprised 35.9% males and 64.1% females, and so the higher proportion of females among the older adults is one possible reason for the statistically insignificant risk of zolpidem in older adults in our population.

This study had several limitations. First, all of the analyzed information regarding comorbidity, prescription, and cause of death was collected from the database originally used for medical claims. There can be discrepancies between actual and registered diagnoses, and quantitative and objective assessments of sleep and mood cannot be performed. Second, zolpidem prescriptions over the entire study period were included, and so exposure to zolpidem was not confined to the period after a brain cancer diagnosis. Third, data related to zolpidem dosage were not available because of regulatory authorities protecting the confidentiality of prescription dosage. However, a previous study found increased mortality even with low-dosage zolpidem (5–130 mg/yr).<sup>1</sup> Fourth, this retrospective cohort study did not control for heterogeneity of the disease status, in terms of pathological classification, stage, disease extent of brain cancer, concurrent treatment, or other medical conditions. Fifth, multicollinearity may be present between depression and antidepressant use or sleep disorder. However, if multicollinearity occurs, it would increase the standard error and result in an increased  $p$  value. This study found that zolpidem was significantly associated with in-

creased mortality among younger adults despite the possibility of multicollinearity being present. Sixth, benzodiazepines, another class of common hypnotics, were not included in this study.

While it was potentially subject to the above-mentioned limitations, our study included all incident cases of brain cancer over a 15-year period, comprising more than 38,000 patients. The study sample is therefore representative of patients with brain cancer in South Korea. A long follow-up period with few follow-up losses is another strength of this study, providing completeness. We also performed a sensitivity analysis with all-cause mortality to minimize the probability of the cause of death producing misleading results. The association between zolpidem exposure and all-cause mortality was consistent with the results of the primary analysis.

In conclusion, zolpidem exposure in patients with brain cancer was associated with brain-cancer-specific mortality in adults aged 18–64 years, regardless of sex, but it was not associated with brain-cancer-specific mortality in the older population aged  $\geq 65$  years. However, data on the prescribed dosage of zolpidem and detailed evaluations of sleep status were not available in this study. Further prospective studies designed for detailed evaluations of sleep characteristics are warranted to understand the mechanism underlying the effect of zolpidem on mortality in patients with brain cancer.

#### Availability of Data and Material

The datasets generated or analyzed during the study are not publicly available due to the Personal Information Protection Act of Korea and regulations of the National Health Insurance Sharing Service but are available from the corresponding author on reasonable request.

#### ORCID iDs

Sungeun Hwang	<a href="https://orcid.org/0000-0003-0813-1315">https://orcid.org/0000-0003-0813-1315</a>
Hyoshin Son	<a href="https://orcid.org/0000-0001-6643-3712">https://orcid.org/0000-0001-6643-3712</a>
Manho Kim	<a href="https://orcid.org/0000-0002-0277-6326">https://orcid.org/0000-0002-0277-6326</a>
Sang Kun Lee	<a href="https://orcid.org/0000-0003-1908-0699">https://orcid.org/0000-0003-1908-0699</a>
Ki-Young Jung	<a href="https://orcid.org/0000-0001-5528-9081">https://orcid.org/0000-0001-5528-9081</a>

#### Author Contributions

Conceptualization: Sungeun Hwang, Ki-Young Jung. Data curation: Sungeun Hwang, Hyoshin Son, Ki-Young Jung. Formal analysis: Sungeun Hwang. Investigation: all authors. Methodology: Sungeun Hwang, Ki-Young Jung. Project administration: Ki-Young Jung. Resources: Ki-Young Jung. Supervision: Ki-Young Jung. Writing—original draft: Sungeun Hwang, Ki-Young Jung. Writing—review & editing: all authors.

#### Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

#### Funding Statement

None

## REFERENCES

- Kripke DF, Langer RD, Kline LE. Hypnotics' association with mortality or cancer: a matched cohort study. *BMJ Open* 2012;2:e000850.
- Belleville G. Mortality hazard associated with anxiolytic and hypnotic drug use in the National Population Health Survey. *Can J Psychiatry* 2010;55:558-567.
- Choi JW, Lee J, Jung SJ, Shin A, Lee YJ. Use of sedative-hypnotics and mortality: a population-based retrospective cohort study. *J Clin Sleep Med* 2018;14:1669-1677.
- Linnet K, Sigurdsson JA, Tomasdottir MO, Sigurdsson EL, Gudmundsson LS. Association between prescription of hypnotics/anxiolytics and mortality in multimorbid and non-multimorbid patients: a longitudinal cohort study in primary care. *BMJ Open* 2019;9:e033545.
- Weich S, Pearce HL, Croft P, Singh S, Crome I, Bashford J, et al. Effect of anxiolytic and hypnotic drug prescriptions on mortality hazards: retrospective cohort study. *BMJ* 2014;348:g1996.
- Hsiao FY, Hsieh PH, Gau CS. Ten-year trend in prescriptions of z-hypnotics among the elderly: a nationwide, cross-sectional study in Taiwan. *J Clin Gerontol Geriatr* 2013;4:37-41.
- Lim YJ, Kim HY, Choi J, Lee JS, Ahn AL, Oh EJ, et al. Potentially inappropriate medications by beers criteria in older outpatients: prevalence and risk factors. *Korean J Fam Med* 2016;37:329-333.
- Lan TY, Zeng YF, Tang GJ, Kao HC, Chiu HJ, Lan TH, et al. The use of hypnotics and mortality - a population - based retrospective cohort study. *PLoS One* 2015;10:e0145271.
- Armstrong TS, Shade MY, Breton G, Gilbert MR, Mahajan A, Scheurer ME, et al. Sleep-wake disturbance in patients with brain tumors. *Neuro Oncol* 2017;19:323-335.
- Jeon MS, Dhillon HM, Agar MR. Sleep disturbance of adults with a brain tumor and their family caregivers: a systematic review. *Neuro Oncol* 2017;19:1035-1046.
- Yavas C, Zorlu F, Ozyigit G, Gurkaynak M, Yavas G, Yuce D, et al. Health-related quality of life in high-grade glioma patients: a prospective single-center study. *Support Care Cancer* 2012;20:2315-2325.
- Chang MC, Chun MH. The effect of hypnotics on sleep quality and cognitive function in patients with brain tumors. *J Korean Neurosurg Soc* 2020;63:261-267.
- Seong SC, Kim YY, Khang YH, Park JH, Kang HJ, Lee H, et al. Data resource profile: the National Health Information Database of the National Health Insurance Service in South Korea. *Int J Epidemiol* 2017;46:799-800.
- MicroData Integrated Service (MDIS) [Internet]. Daejeon: Statistics Korea [cited 2021 May 13]. Available from: <https://mdis.kostat.go.kr/eng/index.do>.
- Greenblatt DJ, Roth T. Zolpidem for insomnia. *Expert Opin Pharmacother* 2012;13:879-893.
- Yang BR, Kim YJ, Kim MS, Jung SY, Choi NK, Hwang B, et al. Prescription of zolpidem and the risk of fatal motor vehicle collisions: a population-based, case-crossover study from South Korea. *CNS Drugs* 2018;32:593-600.
- Donnelly K, Bracchi R, Hewitt J, Routledge PA, Carter B. Benzodiazepines, Z-drugs and the risk of hip fracture: a systematic review and meta-analysis. *PLoS One* 2017;12:e0174730.
- Amerio A, Gálvez JE, Odone A, Dalley SA, Ghaemi SN. Carcinogenicity of psychotropic drugs: a systematic review of US Food and Drug Administration-required preclinical in vivo studies. *Aust N Z J Psychiatry* 2015;49:686-696.
- Kao CH, Sun LM, Liang JA, Chang SN, Sung FC, Muo CH. Relationship of zolpidem and cancer risk: a Taiwanese population-based cohort study. *Mayo Clin Proc* 2012;87:430-436.
- Kripke DF. Hypnotic drug risks of mortality, infection, depression, and cancer: but lack of benefit. *F1000Res* 2016;5:918.
- Jaussett I, Ancelin ML, Berr C, Pérès K, Scali J, Besset A, et al. Hypnotics and mortality in an elderly general population: a 12-year prospective study. *BMC Med* 2013;11:212.