



Marital Status Independently Predicts Glioma Patient Mortality: A Surveillance, Epidemiology, and End Results (SEER) Analysis

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■ **OBJECTIVE:** To examine the impact of marital status on the mortality of patients with primary malignant brain tumors excluding bias from basic characteristics and treatment.

■ **METHODS:** We used the Surveillance, Epidemiology, and End Results program to identify 81,277 patients diagnosed from 2000 through 2016 with the most common primary malignant brain tumors, including glioma, ependymoma, and medulloblastoma. To avoid bias, we used the propensity score matching method to match 44,854 patients with complete clinical and follow-up information. Then, we used Cox regression and Kaplan-Meier survival analysis to investigate the impact of marital status on cancer patient mortality.

■ **RESULTS:** Married patients were more likely to receive surgery and adjuvant chemo- or radiotherapy than single and divorced, separated, and widowed (DSW) patients (all $P < 0.001$). Married patients with high grade glioma were more likely to survive longer and less likely to die of their malignance compared with single (adjusted odds ratio [OR] 1.120; 95% confidence interval [CI], 1.069 to 1.174; $P < 0.001$; OR 1.078; 95% CI, 1.025 to 1.133; $P = 0.003$; respectively), and DSW patients (OR 1.117; 95% CI, 1.074 to 1.161; $P < 0.001$; OR 1.090; 95% CI, 1.046 to 1.136; $P < 0.001$; respectively) (all adjusted to the married group). Similar results were identified in patients with low-grade glioma but not ependymoma and medulloblastoma.

■ **CONCLUSIONS:** Even after adjusting for known confounders, married patients with high-grade glioma and low-grade glioma are at higher possibility to have a better outcome. This study highlights the potential significance that intimate support from spouse can improve glioma patient survival.

INTRODUCTION

Primary malignant brain cancers remain to be devastating disease with little treatment options and poor outcome.

The annual direct health care cost is € 3.2 billion and indirect cost is € 1.9 billion for brain tumor in Europe.¹ The National Institutes of Health/National Cancer Institute spends hundreds of millions of dollars per year on brain cancer research, focused mainly on biological investigation. Given such huge costs for disease treatment and biological investigation, more efforts are put on the study of targeted social support interventions, which have been identified to provide positive effects on the recovery of mental and physiological health and quality of life in cancer patients.

Earlier studies assessed the impact of marital status on the survival of cancer patients and yielded conflicting results with protective,²⁻⁴ mixed,⁵⁻⁷ and nonsignificant^{8,9} effects, due to population selection and analysis bias. Many investigators

Key words

- Glioma
- Marital status
- Outcome
- SEER

Abbreviations and Acronyms

- CI: Confidence interval
- CRM: Cancer-related mortality
- DSW: Divorced, separated, and widowed
- HGG: High-grade glioma
- LGG: Low-grade glioma
- OM: Overall mortality
- OR: Odds ratio
- OS: Overall survival
- PSM: Propensity score matching

SEER: Surveillance, Epidemiology, and End Results

TMZ: Temozolomide

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adjusted demographic factors and tumor-related parameters such as tumor size, stage, and metastasis, and found that marital status was an independent prognostic factor for survival in multiple types of cancers, including glioblastoma.¹⁰⁻¹⁷ Considering that marriage is a complex social factor, not only impacting mental and physiological health but also affecting patient's the way of living, such as smoking, drinking, and decision-making. It was reported that married patients tended to receive more treatments.¹⁷⁻¹⁹ Recently, there was no significant effect of marital status found on patient outcome after adjusting treatment parameters including surgery, chemotherapy, and radiotherapy.²⁰⁻²² In glioblastoma, previous reports found that marriage was a protective factor in glioblastoma patients,^{16,17} however, the authors did not exclude the bias from received treatment in their cohorts of patients, as former investigators did.¹⁰⁻¹⁷ Thus, the impact of marital status on the outcome for glioma patients remains unclear.

Given the significant differences of psychological and physical environment among married, single, separated, divorced, and widowed patients, patients with different marital status might reflect differently and choose different treatments when facing devastating cancer. Hence, such bias might exist in those studies that classified single, separated, divorced, and widowed together as the "unmarried" group.^{2-15,20,23-26}

In the present study, we used the Surveillance, Epidemiology, and End Results (SEER) database to investigate the impact of marital status on the survival of patients with primary malignant brain tumor, including high-grade glioma (HGG), low-grade glioma (LGG), ependymoma, and medulloblastoma by Cox regression and Kaplan-Meier survival analysis. To avoid bias, we introduced propensity score matching (PSM) analysis based on the demographic factors and treatment information.

METHODS

Patient Cohort

We used the SEER database to identify 81,277 patients diagnosed between 2000 and 2016 with one of the most common primary malignant brain tumors, including specified low-grade astrocytic tumors, astrocytoma (not otherwise specified), and other glioma (these 3 types of glioma classified as LGG); glioblastoma and anaplastic astrocytoma (the 2 classified as HGG); and ependymoma and medulloblastoma. This study was conducted in accordance with the policies of the Scientific Ethics Committee of SEER program and Sun Yat-sen University. The pathologic diagnosis was referred to the site recode ICD-O-3/WHO2008 in the SEER database. The year 2000 was selected as the first year of the study given that temozolomide (TMZ) was approved for the treatment of refractory anaplastic astrocytoma by the US Food and Drug Administration in August 1999, and currently TMZ is the chemotherapy drug for the first-line treatment of adult diffuse gliomas.²⁷⁻²⁹

Study Design

As determined by SEER, race was classified as white, African American, and others. Patients with unknown marital status, unmarried, or domestic partner at diagnosis were excluded. The marital status of patients who never married were defined as single, and those divorced, separated, and widowed patients were

classified as DSW group. Thus, the marital status was classified as single, married, and DSW. Patients receiving any type of radiation including beam radiation, radioactive implants, radioisotopes, or combinational radiotherapy were classified as radiation used. Surgery not performed or autopsy only were classified as surgery not performed. Patients were excluded if age at diagnosis was less than 18 years, or clinical information including marital status, race, surgery, radiation, chemotherapy and survival months was incomplete or unknown, leaving 44,854 patients in the final cohort.

Regarding the significant difference in patient basic characteristics, propensity score matching (PSM) analysis was introduced to eliminate selection bias and balance the baseline differences. Propensity score was calculated by patient characteristics including demographic factors (age, sex, race) and treatment information (surgery, radiation and chemotherapy). PSM analysis was performed without replacement using a caliper with a width 0.2 of standard deviation. The matching ratio was indicated in the PSM analysis of each subgroup.

Statistical Analysis

Baseline patient characteristics were compared with the Student's t test or Mann-Whitney U test for each malignancy. Categorical data were presented as percentages and compared with the χ^2 test. Overall mortality (OM) was defined as the time from the diagnosis until death from any cause, and cancer-related mortality (CRM) was defined as the time from diagnosis until death caused by the original brain cancer. Multivariable analyses with the Cox proportional-hazards model were used to assess the impact of marital status on OM and CRM after adjusting basic prognostic factors, including age, sex, race and surgery, and radiation and chemotherapy information. The selected covariates were age, sex, race and surgery, and radiation and chemotherapy. Kaplan-Meier survival analysis was also performed after adjusting basic characteristics, and any difference in survival were evaluated with a stratified log-rank test. Statistical analysis and propensity score matching analysis were carried out using SPSS 22.0 (IBM, Armonk, NY). A P value <0.05 was considered statistically significant.

RESULTS

A total of 44,854 patients were included after exclusion of 36,423 patients. Of this cohort of patients, the number of married, single, and DSW patients was 30,220, 7235, and 7399, respectively. As shown in **Table 1**, patients in single group (median age: 46 ± 17 years) trended to be much younger compared with those married (59 ± 14 years) and DSW patients (65 ± 13 years) ($P < 0.001$). More male patients were found in the married (63.2%) and single groups (60.4%) ($P < 0.001$), which was consistent with a previous epidemiologic study.³⁰ However, there were more female patients in the DSW group (62.5%) ($P < 0.001$). The fact that in general women live longer than men may account for the finding. The single patients presented with a higher incidence of LGG (27.4%) compared with married (18.1%) or DSW (17.1%) patients ($P < 0.001$). The patients in the 3 groups received incomparable rates of treatment, and the married patients had a higher rate of surgery (78.5%), radiation (98.0%), and chemotherapy (74.2%) compared with the other 2

Table 1. Baseline Characteristics Stratified by Marital Status in Patients with Primary Malignant Brain Tumors

Characteristics	Married (n = 30,220)	Single (n = 7235)	DSW (n = 7399)	P Value
Age, years	59 ± 14	46 ± 17	65 ± 14	<0.001
Sex, n (%)				<0.001
Male	19,085 (63.2)	4368 (60.4)	2775 (37.5)	
Female	11,135 (36.8)	2867 (39.6)	4624 (62.5)	
Race				<0.001
White	27,331 (90.4)	5969 (82.5)	6612 (89.4)	
Black	1203 (4.0)	796 (11.0)	503 (6.8)	
Others	1686 (5.6)	470 (6.5)	284 (3.8)	
Pathology				<0.001
HGG	24,239 (80.2)	4830 (66.8)	6040 (81.6)	
LGG	5456 (18.1)	1985 (27.4)	1263 (17.1)	
Ependymoma	304 (1.0)	167 (2.3)	61 (0.8)	<0.001
Medulloblastoma	221 (0.7)	253 (3.5)	35 (0.5)	
Surgery				
Yes	23,723 (78.5)	5830 (80.6)	5451 (73.7)	
No	6497 (21.5)	1405 (19.4)	1948 (26.3)	
Radiation				<0.001
Yes	29,610 (98.0)	7041 (97.3)	7053 (95.3)	
No	610 (2.0)	194 (2.7)	346 (4.7)	
Chemotherapy				<0.001
Yes	22,427 (74.2)	4983 (68.9)	4684 (63.3)	
No	7793 (25.8)	2252 (31.1)	2715 (36.7)	

Values presented as mean ± SD or n (%).
HGG, high-grade glioma; LGG, low-grade glioma.

patient groups ($P < 0.001$). Regarding the significant difference of basic characteristics, treatment information, and pathologic background of each malignancy, we then introduced PSM analysis and investigated the impact of marital status on survival of each malignancy.

Given that the social and family support and personal mental status varied among single, married, and DSW patients, we did subgroup analysis between married and single, married and DSW, and single and DSW for each malignancy. All the basic parameters were well matched in all subgroup analyses (**Supplementary Tables S1–S3**). As displayed in **Table 2**, after adjustment for demographic and treatment information, single patients with HGG and LGG were more likely to die earlier versus those married patients, the odds ratio (OR) and 95% confidence interval (CI) was 1.120, 1.069 to 1.174 ($P < 0.001$); and 1.169, 1.065 to 1.284 ($P = 0.001$), respectively. Also, single patients with HGG (OR 1.078; 95% CI: 1.025 to 1.133; $P = 0.003$) but not LGG (OR 1.083; 95% CI: 0.976 to 1.201; $P = 0.133$) were more likely to die of their malignancy.

Similarly, DSW patients with HGG (OR 1.117; 95% CI: 1.074 to 1.161; $P < 0.001$) and LGG (OR 1.098; 95% CI: 0.997 to 1.209;

$P = 0.057$) were also less likely to survive longer than married patients (**Table 3**). Only the DSW patients with HGG were presented with higher risk of die of their disease (OR 1.090; 95% CI, 1.046 to 1.136; $P < 0.001$) (**Table 3**). Moreover, single patients and DSW patients showed comparable hazard ratios of OM and CRM in HGG ($P = 0.208$ and $P = 0.113$, respectively) and LGG ($P = 0.788$ and $P = 0.915$, respectively) (**Supplementary Table S4**). However, no significant protective effect of marital status on OM and CRM were found in patients with ependymoma and medulloblastoma (**Tables 2 and 3**).

On the basis of Kaplan-Meier survival analysis, single HGG patients had longer overall survival (OS) (median OS: 11 vs. 10 months, $P = 0.002$) compared with married HGG patients (**Figure 1A**), which implied that factors other than marriage impact HGG patient outcome. Consistently, the married HGG patients presented longer overall survival ($P < 0.001$) and lower cancer-related death ($P < 0.001$) than their DSW counterparts (**Figure 1C and D**). For the LGG patients, the married patients survived longer than both single and DSW patients ($P < 0.001$ and $P = 0.014$, respectively) (**Figure 2A and C**). No significant differences in overall survival and cancer-related death were

Table 2. Hazard Ratios for Overall Mortality and Cancer-Related Mortality in Single Patients Compared With Married Patients in Primary Brain Malignance

Malignance	Overall Mortality		Cancer-Related Mortality	
	P Value	OR (95% CI)	P Value	OR (95% CI)
HGG	<0.001	1.120 (1.069–1.174)	0.003	1.078 (1.025–1.133)
LGG	0.001	1.169 (1.065–1.284)	0.133	1.083 (0.976–1.201)
Ependymoma	0.084	1.677 (0.934–3.013)	0.170	1.637 (0.810–3.307)
Medulloblastoma	0.092	1.562 (0.929–2.627)	0.200	1.525 (0.800–2.907)

CI, confidence interval; OR, odds ratio; HGG, high-grade glioma; LGG, low-grade glioma.

found between single and DSW patients with either HGG or LGG (**Supplementary Table S4**).

DISCUSSION

First, we found that married patients were more likely to receive surgery and adjuvant chemotherapy or radiotherapy than single and DSW patients, and the DSW patients were the population that received significant less surgical, chemotherapy, and radiotherapy treatment than the other 2 populations (**Table 1**), which is consistent with reports from previous studies.^{17–19} Second, unmarried patients, including those who are single and DSW patients, were at significantly greater risk of short OS and death from cancer compared with married patients. The positive association between marital status and patient outcome was significant only in LGG and HGG, however—not in ependymoma and medulloblastoma (**Tables 2 and 3; Figures 1 and 2**). Third, the single and DSW patients showed comparable overall mortality and cancer-related mortality in HGG and LGG (**Supplementary Table S4**).

Previously, Chang et al. reported that unmarried patients with glioblastoma had a shorter survival compared with married patients.¹⁷ Xie et al. also found a tight association of marital status with patient survival in glioblastoma¹⁶ and astrocytoma¹⁹ after adjustment of several parameters by PSM analysis. In their studies, basic characteristics, including age, race, registry sites,

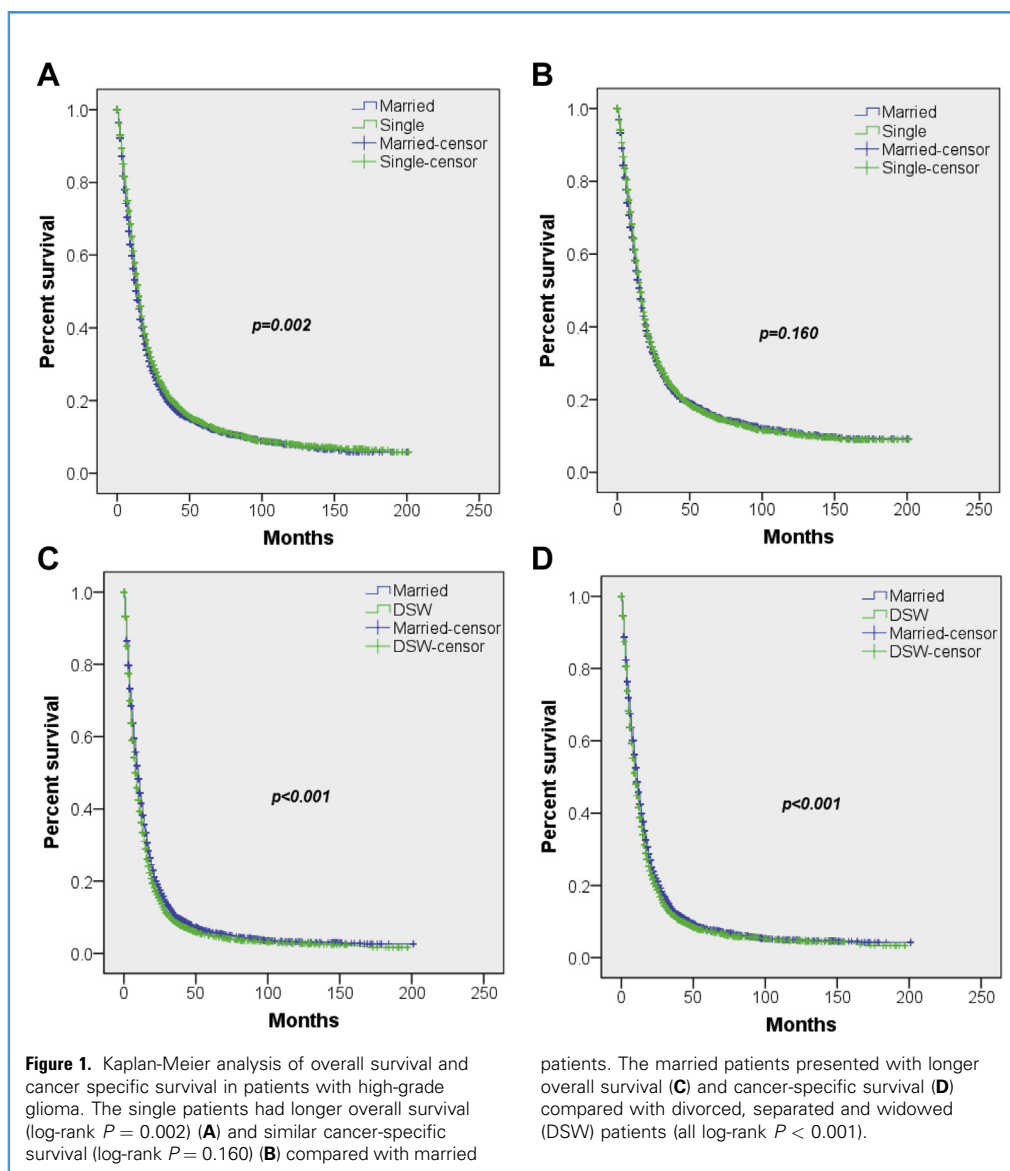
diagnosis year, insurance recode, surgery performance, tumor size, and metastasis, but not treatment patterns, were included to exclude bias. As reported, those factors were correlated with treatment patterns and patient outcome, however, treatments including surgery, chemotherapy, and radiotherapy were much more important and independent factors correlated with glioma patient survival according to previous reports and guidelines.^{27–29} Therefore, it is extremely important to exclude bias from treatment patterns when investigating the impact of marital status on glioma patient survival. In the present study, we selected basic characteristics and treatment parameters to exclude bias by PSM analysis.

There is still significant correlation between marital status and outcome of patients in HGG by subgroup analysis among married, single, and DSW patients (**Tables 2 and 3; Figures 1 and 2**). The findings in the present study indicate that intimate support from spouse—but not parents, children, or friends—might impede HGG progression and hence benefit patient outcome. There are many explanations for the vital question of why marriage benefits cancer patient survival, but the most likely reasons are disease- and treatment-related. First, married patients are usually admitted at the earlier stages compared with unmarried patients.¹⁰ Glioma patients at earlier stages present with better physical status and higher Karnofsky Performance Scale score, which are reportedly associated with lower mortality and morbidity in glioblastoma and astrocytoma.^{31–33} Better adherence

Table 3. Hazard Ratios for Overall Mortality and Cancer-Related Mortality in DSW Patients Compared With Married Patients in Primary Brain Malignance

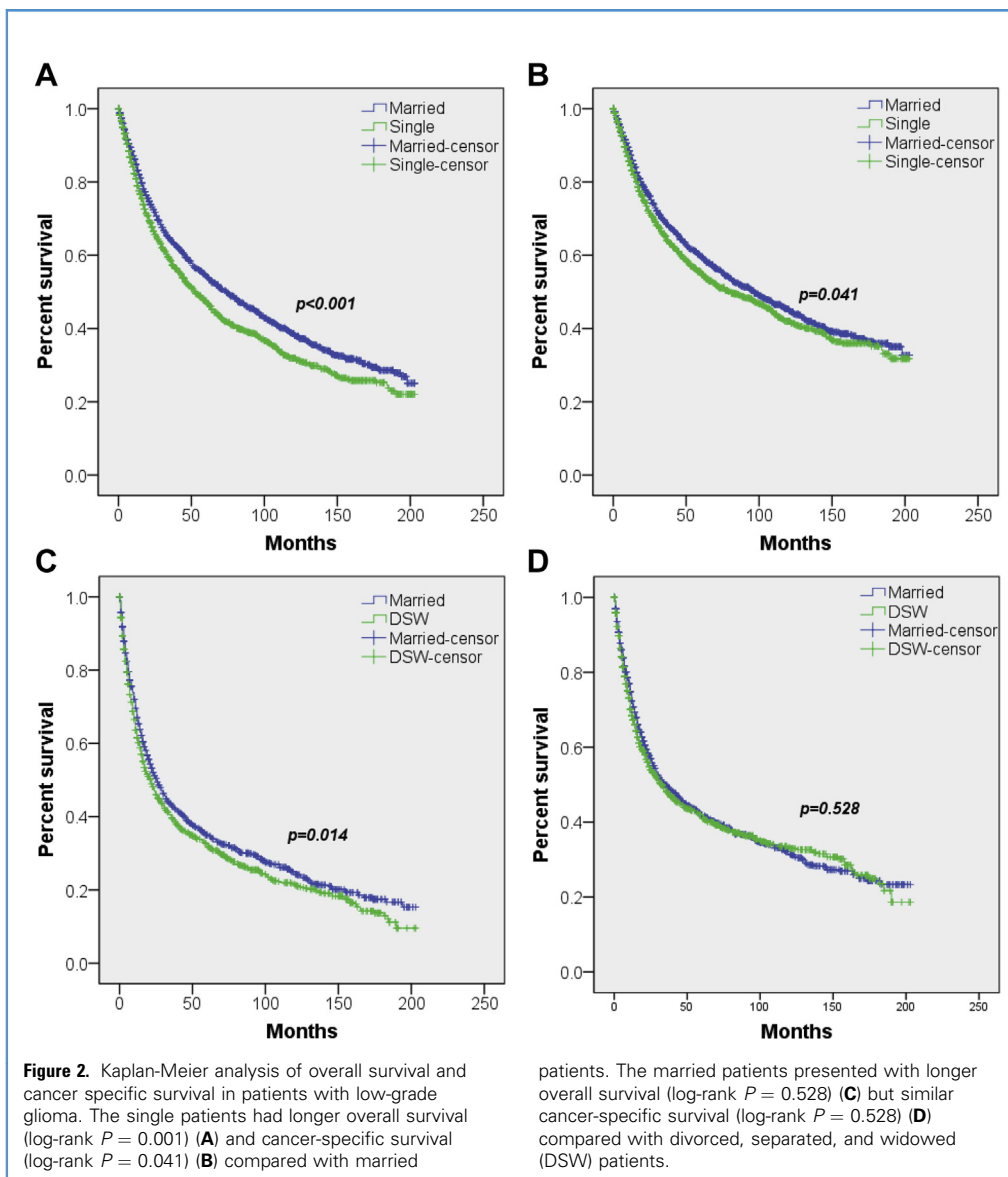
Malignance	Overall Mortality		Cancer-Related Mortality	
	P Value	OR (95% CI)	P Value	OR (95% CI)
HGG	<0.001	1.117 (1.074–1.161)	<0.001	1.090 (1.046–1.136)
LGG	0.057	1.098 (0.997–1.209)	0.869	1.009 (0.905–1.125)
Ependymoma	0.978	1.009 (0.523–1.947)	0.882	1.065 (0.466–2.431)

CI, confidence interval; OR, odds ratio; HGG, high-grade glioma; LGG, low-grade glioma.



to prescribed treatments in married patients was another important reason.³⁴ Impaired adherence had been associated with poorer outcome in cancer patients, as some have reported that the appropriate time window of initiation of radiation was critical for glioma patient outcome.³⁵⁻³⁷ Moreover, married patients displayed positive outlook with less distress, depression, and anxiety than their unmarried counterparts, as their spouse can share the emotional burden and provide appropriate social support. Less emotional pressure was a mediator between marital status and treatment adherence.³⁸ Also, depression was reported to be correlated to poorer treatment response, and behavior activation therapy showed efficacy in cancer patients with severe depression.³⁹

However, marriage is only correlated with overall mortality but not cancer-related mortality in LGG (Tables 2 and 3; Figures 1 and 2). The difference of the correlation of marriage and cancer-related mortality between HGG and LGG implies that there are treatment-unrelated factors mediating the protective effect of marriage on LGG mortality. For example, marriage could strongly influence patient life habits such as smoking, drinking, and diet control. Limited efficacy of chemotherapy and radiotherapy in LGG might be another possible explanation for the difference. Because of the limited number of cases, we were unable to do PSM match analysis and investigate the impact of marital status on patient mortality in the unmarried cohorts stratified among



their respective components including single, separated, divorced, and widowed. Also, we did not find a survival difference among single, married, and DSW patients with ependymoma and medulloblastoma. The higher incidence of the 2 types of cancers in younger adults and children^{40,41} and the fact that these 2 populations are less likely to be married might be possible reasons.

The study is subject to several other limitations, such as inherent limitations of retrospective study. The treatment patterns might vary from each patient and doctor, and the “standard” treatments differ from each year or each version of the guidelines. In addition, insurance status, the quality of marital status, and the mental pressure from family and society are unknown and not included in this study.

CONCLUSIONS

Notwithstanding these limitations, data from present study prove that marital status independently correlates with the outcome of glioma patients, especially those with more aggressive HGG. The supports from an intimate spouse play an important role in improving cancer patient outcome.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Zhong Deng: Investigation, Formal analysis, Writing - original draft. **Xixi Li:** Investigation, Formal analysis, Writing - original draft. **Jia Yang:** Visualization. **Hai Yu:** Conceptualization, Writing - review & editing, Investigation, Methodology. **Nu Zhang:** Methodology, Investigation, Writing - review & editing, Conceptualization.

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Conflict of interest statement: The authors declare that the article content was composed in the absence of any

commercial or financial relationships that could be construed as a potential conflict of interest. The data access is approved by the SEER program and the usage is in accordance to the policies of SEER program.

Availability of Data and Material: In the present study, all data were selected from the Surveillance, Epidemiology, and End Results (SEER) database. Researchers can request and obtain access to the data at <https://seer.cancer.gov>.

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SUPPLEMENTARY DATA

Supplementary Table S1. Baseline Characteristics Between Matched Married and Single Patients With Primary Malignant Brain Tumors by PSM Analysis

Characteristics	HGG (1:1)			LGG (1:1)			Ependymoma (1:1)			Medulloblastoma (1:1)		
	Married (n = 4415)	Single (n = 4415)	P Value	Married (n = 1618)	Single (n = 1618)	P Value	Married (n = 89)	Single (n = 89)	P Value	Married (n = 105)	Single (n = 105)	P Value
Age (years), mean \pm sd	53.5 \pm 14.3	53.5 \pm 14.0		42.6 \pm 13.7	42.3 \pm 14.2		41.0 \pm 13.9	41.3 \pm 14.3		31.5 \pm 8.6	31.5 \pm 8.6	
Sex (male), n (%)	2690 (60.9)	2661 (60.3)	0.528	933 (57.7)	936 (57.8)	0.915	54 (60.7)	53 (59.6)	0.878	68 (64.8)	73 (69.5)	0.463
Race, n (%)			<0.001			<0.001			0.295			0.043
White	3704 (83.9)	3747 (84.9)		1401 (86.6)	1346 (83.2)		76 (85.4)	72 (80.9)		96 (91.4)	94 (89.5)	
Black	474 (10.7)	382 (8.7)		79 (4.9)	172 (10.6)		6 (6.7)	12 (13.5)		5 (4.8)	11 (10.5)	
Others	237 (5.4)	286 (6.5)		138 (8.5)	100 (6.2)		7 (7.9)	5 (5.6)		4 (3.8)	0 (0)	
Surgery, n (%)	3655 (82.8)	3669 (83.1)	0.692	1144 (70.7)	1150 (71.1)	0.816	85 (95.5)	86 (96.6)	0.700	104 (99.0)	105 (100.0)	0.316
Radiation, n (%)	4284 (97.0)	4302 (97.4)	0.243	1591 (98.3)	1571 (97.1)	0.019	88 (98.9)	88 (98.9)	1.000	105 (100.0)	104 (99.0)	0.316
Chemotherapy, n (%)	3391 (76.8)	3321 (75.2)	0.081	843 (52.1)	977 (60.4)	<0.001	11 (12.4)	13 (14.6)	0.661	66 (62.9)	65 (61.9)	0.887

Supplementary Table S2. Baseline Characteristics Between Matched Married and DSW Patients With Primary Malignant Brain Tumors by PSM Analysis

Characteristics	HGG (1:1)			LGG (1:1)			Ependymoma (1:1)		
	Married (n = 5740)	DSW (n = 5740)	P Value	Married (n = 1175)	DSW (n = 1175)	P Value	Married (n = 50)	DSW (n = 50)	P Value
Age (years), mean \pm sd	65.2 \pm 12.1	65.2 \pm 12.2		56.5 \pm 15.3	57.2 \pm 15.8		51.8 \pm 13.4	52.2 \pm 12.9	
Sex (male), n (%)	2259 (39.4)	2249 (39.2)	0.848	490 (41.7)	497 (42.3)	0.770	17 (34.0)	17 (34.0)	1.000
Race, n (%)			0.001			<0.001			0.013
White	5210 (90.8)	5110 (89.0)		1096 (93.3)	1045 (88.9)		49 (98.0)	41 (82.0)	
Black	305 (5.3)	402 (7.0)		37 (3.1)	87 (7.4)		0 (0)	8 (16.0)	
Others	225 (3.9)	228 (4.0)		43 (3.6)	43 (3.7)		1 (2.0)	1 (2.0)	
Surgery, n (%)	4462 (77.7)	4399 (76.6)	0.161	712 (60.6)	731 (62.2)	0.421	50 (100)	49 (98.0)	0.315
Radiation, n (%)	5503 (95.9)	5540 (96.5)	0.071	1131 (96.3)	1145 (97.4)	0.098	50 (100)	49 (98.0)	0.315
Chemotherapy, n (%)	3949 (68.7)	3989 (69.5)	0.419	587 (50.0)	603 (51.3)	0.509	1 (2.0)	2 (4.0)	0.558

Supplementary Table S3. Baseline Characteristics Between Matched Single and DSW Patients With HGG and LGG by PSM Analysis

Characteristics	HGG (1:1)			LGG (1:1)		
	Single (n = 3146)	DSW (n = 3146)	P Value	Single (n = 799)	DSW (n = 799)	P Value
Age (years), mean \pm sd	59.1 \pm 11.6	58.8 \pm 11.7		50.5 \pm 13.7	50.7 \pm 15.9	
Sex (male), n (%)	1713 (54.5)	1485 (47.2)	<0.001	420 (52.6)	411 (51.4)	0.652
Race, n (%)			<0.001			0.614
White	2715 (86.3)	2613 (83.1)		701 (87.7)	689 (86.2)	
Black	312 (9.9)	337 (10.7)		66 (8.3)	71 (8.9)	
Others	119 (3.8)	196 (6.2)		32 (4.0)	39 (4.9)	
Surgery, n (%)	2593 (82.4)	2530 (80.4)	0.041	538 (67.3)	520 (65.1)	0.341
Radiation, n (%)	3043 (96.7)	3028 (96.2)	0.304	780 (97.6)	777 (97.2)	0.635
Chemotherapy, n (%)	2346 (74.6)	2333 (74.2)	0.707	417 (52.2)	448 (56.1)	0.120

Supplementary Table S4. Hazard Ratios for Overall Mortality and Cancer-Related Mortality in DSW Patients Compared With Single Patients in Primary Brain Malignance

Malignance	Overall Mortality		Cancer-Related Mortality	
	<i>P</i> Value	OR (95% CI)	<i>P</i> Value	OR (95% CI)
HGG	0.208	0.966 (0.915–1.019)	0.113	0.954 (0.901–1.011)
LGG	0.788	1.017 (0.900–1.150)	0.915	1.008 (0.876–1.159)