Pediatric Glioma Outcomes: Predictors of Early Mortality

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OBJECTIVE: **To assess the early mortality in pediatric glioma and identify predictors of early mortality, which may provide insight into the therapeutic strategies for children with a high risk of early mortality.**

METHODS: **We used SEER*Stat 8.3.5 software to extract data of pediatric glioma from the Surveillance, Epidemiology, and End Results database. Logistical regression to identify the independent factors in predicting early mortality.**

RESULTS: **A total of 3035 male and 2741 female patients were enrolled in the present study. The death rates within 1 month and 3 months after diagnosis were 1.32% and 2.44%, respectively. Early mortality decreased significantly during the past 40 years. Our results showed that glioblastoma, anaplastic glioma, and oligodendroglioma were risk factors of early mortality for children diagnosed with glioma, whereas advanced age, gross total resection, radiation, and chemotherapy were associated with decreased early mortality.**

CONCLUSIONS: **We found a decrease in early mortality during the past 40 years. The death rates within 1 month and 3 months after diagnosis were 1.32% and 2.44%, respectively. Age at diagnosis, histologic subtype, the extent of resection, chemotherapy, and radiation were associated with early mortality in pediatric glioma.**

Key words
- Early mortality
- End Results
- Epidemiology
- Pediatric glioma
- Predictors
- Surveillance

Abbreviations and Acronyms
CI: Confidence interval
DA: Diffuse astrocytoma
EOR: Extent of resection
OR: Odds ratio
PA: Pilocytic astrocytoma
SEER: Surveillance, Epidemiology, and End Results

INTRODUCTION

Glioma is a common cause of cancer-related mortality in children that accounts for approximately 30% of all pediatric brain tumors.[1] Glioma is classified into grade I (pilocytic astrocytoma [PA]), grade II (diffuse astrocytoma [DA] and oligodendroglioma), grade III (anaplastic astrocytoma and anaplastic oligodendroglioma), and grade IV (glioblastoma multiforme and diffuse midline glioma) according to the latest classification standard of the World Health Organization.[2] Although significant improvement in diagnosis and therapeutic interventions has substantially increased the overall survival of pediatric glioma, the clinical outcome of the children survivors diagnosed with glioma remains poor, including low quality of life, significant comorbidities, and increased mortality.[3-11] In addition, morbidity and mortality vary greatly within histopathologic subtypes.[12] However, most published studies primarily have focused on long-term clinical outcomes of pediatric glioma[4,9,10,12] but not early mortality. As a result, little is known about the early mortality in children with glioma. To address this issue, we extracted information on pediatric glioma from the Surveillance, Epidemiology, and End Results (SEER) database to assess the early mortality in pediatric glioma and identify predictors of early mortality, which may provide insight into the therapeutic strategies for children with a high risk of early mortality.

METHODS

Patients

We used SEER*Stat 8.3.5 software (National Cancer Institute, Bethesda, Maryland, USA) to extract data of pediatric glioma from the SEER database. *International Classification of Diseases for Oncology,*

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Table 1. Characteristics of Pediatric Glioma

Characteristics	Full Cohort, n	1-Month Death, *n*	3-Month Death, *n*
Sex			
Male	3035	38	75
Female	2741	38	66
Age, years			
0–3	1134	27	44
4–7	1684	15	33
8–14	1507	10	23
15–18	1451	24	41
Race			
White	4637	64	114
Black	639	8	16
Others	500	4	11
Year of diagnosis			
1975–1984	266	7	12
1985–1994	670	11	21
1995–2004	1834	25	42
2005–2010	1540	17	36
2011–2016	1466	16	30
Tumor location			
Frontal	456	9	16
Temporal	474	6	11
Parietal	243	6	10
Occipital	77	1	2
Ventricular	271	5	7
Cerebrum	648	9	22
Cerebellum	1545	4	8
Brainstem	653	9	19
Spinal cord	240	2	2
Optic nerve	153	2	6
Others	1016	23	38
Histology			
Pilocytic astrocytoma	3769	18	25
Diffuse astrocytoma	270	2	4
Glioblastoma	753	39	76
Anaplastic glioma	598	9	28
Oligodendroglioma	386	8	8
Extent of resection			
Total gross resection	1880	11	16
Subtotal resection	1064	14	31
Biopsy	1471	31	53
Unknown	1361	20	41
Radiotherapy			
Yes	1106	1	12
No	4670	75	129
Chemotherapy			
Yes	1507	5	24
No	4269	71	117

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3rd Edition codes 9420, 9450, 9411, 9451, 9440, and 9421 were used to identify DA, oligodendroglioma, anaplastic glioma, glioblastoma, and PA. A patient is eligible for enrollment if 1) diagnosis of glioma was a positive confirmation; 2) survival information is available; and 3) they are between 0 and 18 years of age.

Definition of Early Mortality

In the present study, early mortality included 1-month mortality and 3-month mortality. The proportion of patients who died within 1 and 3 months were used to estimate the 1-month death rate and 3-month death rate, respectively.

Parameters

The variables identified into analysis included sex (male and female), age (0–3, 4–7, 8–14, and 15-18 years old), race (white, black and others), year of diagnosis (1975–1984, 1985–1994, 1995–2004, 2005–2010, and 2011–2016), tumor location, histologic subtypes, extent of resection (EOR), radiotherapy (yes and no), and chemotherapy (yes and no). The tumor location included cerebrum, frontal, temporal, parietal, occipital, cerebrum, ventricle, cerebellum, brainstem, spinal cord, optic nerve, and others. To convince the statistics, the histologic subtype was Q2 classified into PA, DA, oligodendroglioma, anaplastic glioma, and glioblastoma. EOR was categorized as biopsy, gross total resection, subtotal resection, and unknown.

Statistical Analysis

All statistical analyses were conducted using the Statistical Package for the Social Sciences, version 19.0 (IBM Corp., Armonk, New York, USA). A descriptive analysis of the basic characteristics of patients enrolled was performed. We used logistical regression to identify the independent factors in predicting early mortality. The statistical significance was defined as a P value of less than 0.05 with 2 sides.

RESULTS

A total of 3035 male and 2741 female patients were enrolled in the present study. Table 1 summarizes the demographic and clinical characteristics of pediatric glioma. The median age at diagnosis was 9 years, 80.28% of patients were white, and 52.04% were diagnosed between 2005 and 2016. For all tumors, the most

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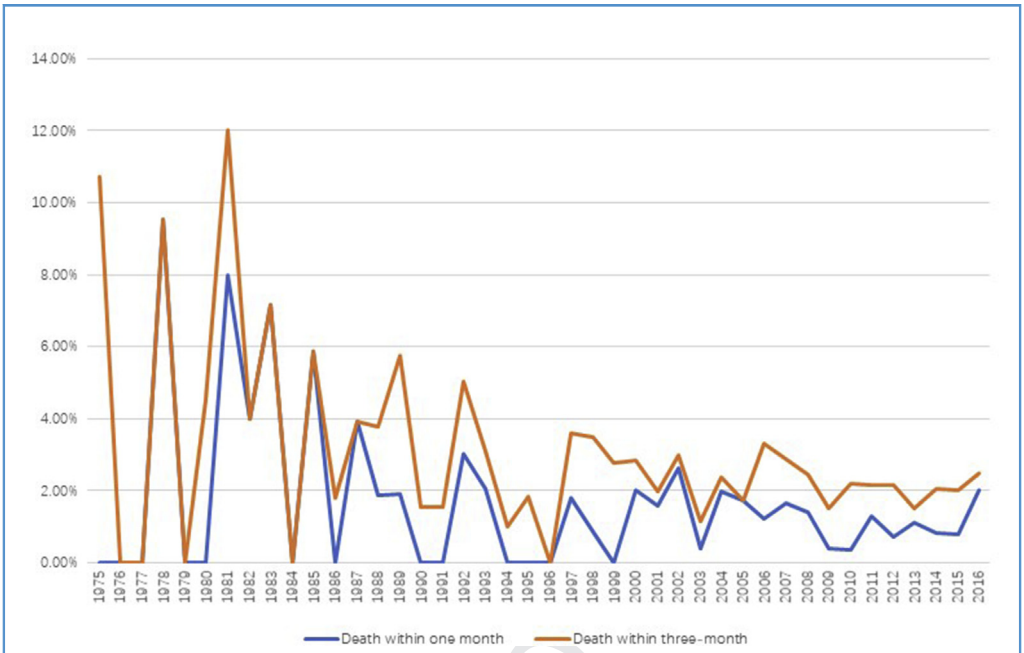

Figure 1. One- and three-month mortality (%) of pediatric glioma by year of diagnosis.

common tumor location was cerebellum (26.74%), followed by others (17.59%), brainstem (11.31%), cerebrum (11.21%), temporal lobe (8.21%), frontal lobe (7.89%), ventricle (4.69%), parietal lobe (4.21%), spinal cord (4.15%), optic nerve (2.65%), and occipital lobe (1.33%). Among all patients, 65.25% of tumors were PA, 13.04% were glioblastoma, 10.35% were anaplastic glioma, 6.68% were oligodendroglioma, and 4.67% were DA. Biopsy, gross total resection, subtotal resection, and unknown EOR were identified in 25.27%, 32.55%, 18.42%, 23.56% of cases, respectively. Radiotherapy and chemotherapy were administered in 19.15% and 26.09% of cases, respectively. The death rates within 1 month and 3 months after diagnosis were 1.32% and 2.44%, respectively.

We first assessed time trends for death rates within 1 month and 3 months after diagnosis. Early mortality decreased significantly during the past 40 years (Figure 1). The greatest mortality within 1 month was 9.52% in 1978, and mortality within the first month in 2016 was 2%. Furthermore, the greatest death rate within 6 months following diagnosis was 12% in 1981, whereas the mortality within the first month in 2016 was 2.5%.

We next examined the factors associated with early mortality in pediatric glioma (Tables 1 and 2). Our results showed that factors including age, histologic subtype, EOR, radiation, and chemotherapy were associated with early mortality in children diagnosed with glioma. We used patients aged 0–3 years as the reference category; individuals aged 4–7 and 8–14 years showed a significantly greater risk of early death within 1 month (0.89%, and 0.66% vs. 2.38%%). The adjusted odds ratio (ORs) of 1-month mortality for patients aged 4–7 years and 8–14 years were 0.453 (95% confidence interval [CI] 0.225–0.913) and 0.317 (95% CI 0.144–0.700), respectively. However, the comparison of death rate within 1 month between patients aged 0–3 years and 15–18 years did not reach statistical significance ($P > 0.05$). Furthermore, patients aged 4–7, 8–14, and 15–18 years had high odds of death within 3 months compared with patients aged 0–3 years (1.96%, 1.53%, 2.83% vs. 3.88%). The adjusted ORs of 1-month mortality for patients aged 4–7, 8–14, and 15–18 years were 0.549 (95% CI 0.325–0.929), 0.380 (95% CI 0.213–0.675), and 0.579 (0.348–0.965), respectively. In addition, tumor subtype was also associated with early mortality in pediatric glioma. Patients diagnosed with anaplastic glioma, glioblastoma, and oligodendroglioma had a high probability of death in the first month after diagnosis compared with patients with PA (1.51%, 5.18%, and 2.07% vs. 0.48%). The adjusted ORs of 1-month mortality for patients with anaplastic glioma, glioblastoma, oligodendroglioma were 7.842 (95% CI 3.197–19.235), 36.502 (95% CI 18.340–72.651), and 3.769 (95% CI 1.442–9.849), respectively. We also observed similar findings for the evaluation of histologic subtypes associated with 3-month mortality. Patients received gross total resection had lower odds of death within 1 and 3 months compared with patients experienced biopsy (0.59% vs. 2.11%; 0.85% vs. 3.01%). Gross total resection was also an independent predictor of early mortality for children diagnosed with glioma ($P < 0.05$). Furthermore, chemotherapy and radiation were independent factors in predicting low early mortality (all $P < 0.05$).

DISCUSSION

For the first time, we performed a retrospective study by using the SEER database to evaluate the early mortality and identify factors associated with early death in children diagnosed with glioma. We observed a decrease in early mortality during the past 40 years. The death rates within 1 month and 3 months after diagnosis were 1.32% and 2.44%. Our results showed that glioblastoma,

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Table 2. The Univariate Analysis of Early Mortality in Children with Glioma

	Death within 1 Month		Death within 3 Months	
Characteristics	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
Sex				
Male	Ref	1	Ref	1
Female	0.902 (0.574–1.418)	0.655	1.027 (0.735–1.435)	0.876
Age, years				
0–3	Ref	1	Ref	1
4–7	0.368 (0.195–0.696)	0.002	0.495 (0.313–0.783)	0.003
8–14	0.274 (0.132–0.568)	0.001	0.384 (0.230–0.640)	<0.001
15–18	0.690 (0.396–1.202)	0.19	0.720 (0.467–1.110)	0.137
Race				
White	Ref	1	Ref	1
Black	0.906 (0.432–1.898)	0.739	1.019 (0.600–1.731)	0.945
Others	0.576 (0.209–1.589)	0.287	0.892 (0.477–1.669)	0.722
Year of diagnosis				
1975–1984	Ref	1	Ref	1
1985–1994	0.618 (0.237–1.611)	0.324	0.685 (0.332–1.413)	0.306
1995–2004	0.511 (0.219–1.194)	0.121	0.496 (0.258–0.955)	0.036
2005–2010	0.413 (0.170–1.006)	0.051	0.507 (0.260–0.987)	0.046
2011–2016	0.408 (0.166–1.002)	0.051	0.442 (0.223–0.875)	0.019
Tumor location				
Frontal	Ref	1	Ref	1
Temporal	0.506 (0.162–1.587)	0.243	0.554 (0.232–1.322)	0.183
Parietal	0.795 (0.280–2.261)	0.667	0.847 (0.378–1.897)	0.687
Occipital	0.654 (0.082–5.232)	0.689	0.733 (0.165–3.255)	0.683
Ventricular	0.934 (0.310–2.815)	0.903	0.729 (0.296–1.796)	0.492
Cerebrum	0.700 (0.276–1.776)	0.452	0.966 (0.502–1.861)	0.919
Cerebellum	0.129 (0.040–0.421)	0.001	0.143 (0.061–0.337)	<0.001
Brainstem	0.694 (0.23–1.762)	0.442	0.827 (0.419–1.620)	0.575
Spinal cord	0.417 (0.089–1.947)	0.266	0.705 (0.272–1.826)	0.705
Optic nerve	0.658 (0.141–3.078)	0.595	0.364 (0.083–1.603)	0.182
Others	1.150 (0.528–2.506)	0.724	1.069 (0.589–1.937)	0.827
Histology				
Pilocytic astrocytoma	Ref	1	Ref	1
Diffuse astrocytoma	1.555 (0.359–6.737)	0.555	2.252 (0.778–6.518)	0.134
Glioblastoma	11.383 (6.475–20.011)	<0.001	16.812 (10.621–26.611)	<0.001
Anaplastic glioma	3.184 (1.424–7.121)	0.005	7.357 (4.259–12.706)	<0.001
Oligodendroglioma	4.410 (1.905–10.211)	0.001	3.170 (1.420–7.076)	0.005
Extent of resection				
Biopsy	Ref	1	Ref	1

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Table 2. Continued

Characteristics	Death within 1 Month		Death within 3 Months	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Total gross resection	0.273 (0.137–0.546)	<0.001	0.230 (0.131–0.403)	<0.001
Subtotal resection	0.619 (0.328–1.170)	0.14	0.803 (0.512–1.260)	0.339
Unknown	0.693 (0.393–1.21)	0.205	0.831 (0.549–1.258)	0.381
Radiotherapy				
No	Ref	1	Ref	1
Yes	0.055 (0.008–0.399)	0.004	0.386 (0.213–0.700)	0.002
Chemotherapy				
No	Ref	1	Ref	1
Yes	0.197 (0.079–0.488)	<0.001	0.574 (0.369–0.895)	0.014

OR, odds ratio; CI, confidence interval.

anaplastic glioma, and oligodendroglioma were risk factors of early mortality for children diagnosed with glioma, whereas advanced age, gross total resection, radiation, and chemotherapy were associated with low early mortality.

Although previous research assessed the prognosis of patients with pediatric glioma, most studies focused on overall survival and not specifically on early mortality or factors associated with early death.[4,9,12] Our previous study showed that the death rates within 1 and 3 months after diagnosis of adult glioma were 9.24% and 19.15%, respectively, which were greater than the corresponding early mortality of pediatric glioma presented in this study.[13] The distribution of tumor subtypes between children and adults may be responsible for this substantial variability of early mortality in children and adult patients. Glioblastoma was the most common histologic subtype of glioma for adult patients,[13] whereas PA accounted for 65.25% of all pediatric gliomas. In the present study, we found a decrease in early mortality during the past 40 years, which may be correlated with the improvement in the diagnosis and therapeutic interventions, such as awake surgery,[14] intraoperative magnetic resonance imaging,[15] and tumor treating fields.[16] Tumor resection remains the initial option for pediatric glioma, and gross total resection should be performed for children with tumor location in cerebral hemispheres and the cerebellum,[7,17] which may improve the prognosis. EOR was an important predictor of pediatric glioma.[18,19] Patients experienced gross total resection had a 10-year progression-free survival of 100%, whereas patients underwent subtotal resection had 67%–81%.[18] However, the impact of resection on early mortality of pediatric glioma remained unknown. In the presented study, children who underwent gross total resection had lower odds of early mortality than children who received biopsy (death within 1 month: 0.58% vs. 2.11%; death within 3 months: 0.85% vs. 3.60%). Gross total resection may eliminate tumor-related mass effects and rapidly improve neurologic symptoms. For children diagnosed with high-grade glioma, gross total resection may prolong the window time of radiotherapy and chemotherapy become effective, which may decrease the proportion of early death. Furthermore, we also observed that radiation and chemotherapy were associated with decreased early mortality in pediatric glioma. The findings that chemotherapy and radiation were associated with a favorable prognosis was especially interesting, as those treatments might have been given with palliative intent. Our results emphasized that initial chemotherapy or radiotherapy following gross total resection may be more appropriate and associated with greater benefit to the children with high-grade glioma.

The important effect of tumor subtype also was apparent in our results. The subtype with the greatest early mortality after diagnosis was glioblastoma, followed by anaplastic glioma, oligodendroglioma, and PA. At 1 month after diagnosis, Q3 children with glioblastoma had 33.502 greater odds of death compared with patients with PA. Anaplastic glioma and oligodendroglioma also had 7.842 and 3.769 greater odds of death during the first month when compared with PA. The current evidence also showed that the survival of pediatric glioma was influenced by histologic subtype,[20] which was consistent with our results. The prognostic role of age in pediatric glioma has been reported by several studies.[21-23] In our study, the results showed that children aged 4–7 and 8–14 years showed significantly greater odds of early death compared with patients aged 0–3 years. Furthermore, patients aged 15–18 years had high odds of death within 3 months but not death within 1 month when used patients aged 0–3 years as the reference category. Previous studies have indicated that children with advance age have a poor survival benefit,[22,24] which was consistent with our result that advanced age was a risk factor of early mortality after tumor resection. Our results suggest the potential undertreatment of pediatric patients and the urgent the need to develop specialized clinical and research programs for pediatric cancer patients with high risk of early death, because these patients do not live enough to receive a standardized Q4 treatment or take part in clinical trials.

The strength of our study is that we first provide the real-world data of the early deaths in a large number of patients with

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Table 3. Multivariate Analysis of Early Mortality in Children with Glioma

	Death within 1 Month				Death within 3 Months			
			95% CI				95% CI	
Characteristics	*P* Value	OR	Low CI	High CI	*P* Value	OR	Low CI	High CI
Sex								
Male	1	Ref	Ref	Ref	1	Ref	Ref	Ref
Female	0.390	0.801	0.483	1.328	0.776	0.946	0.647	1.383
Age, years								
0–3	1	Ref	Ref	Ref	1	Ref	Ref	Ref
4–7	0.027	0.453	0.225	0.913	0.025	0.549	0.325	0.929
8–14	0.004	0.317	0.144	0.700	0.001	0.380	0.213	0.675
15–18	0.152	0.628	0.332	1.188	0.036	0.579	0.348	0.965
Race								
White	1	Ref	Ref	Ref	1	Ref	Ref	Ref
Black	0.504	0.761	0.341	1.697	0.339	0.751	0.417	1.351
Other	0.529	1.332	0.545	3.258	0.323	1.420	0.708	2.846
Year of diagnosis								
1975–1984	1	Ref	Ref	Ref	1	Ref	Ref	Ref
1985–1994	0.854	1.108	0.373	3.292	0.642	1.219	0.529	2.807
1995–2004	0.316	0.423	0.079	2.268	0.932	1.045	0.376	2.906
2005–2010	0.270	0.363	0.060	2.196	0.686	1.262	0.408	3.901
2011–2016	0.270	0.365	0.061	2.190	1.000	1.000	0.325	3.080
Tumor location								
Frontal	1	Ref	Ref	Ref	1	Ref	Ref	Ref
Temporal	0.426	0.606	0.177	2.077	0.538	0.742	0.286	1.922
Parietal	0.743	0.826	0.263	2.595	0.722	0.850	0.346	2.088
Occipital	0.616	0.560	0.058	5.378	0.905	0.904	0.170	4.804
Ventricle	0.338	1.831	0.532	6.307	0.500	1.419	0.514	3.918
Cerebellum	0.095	0.327	0.088	1.214	0.158	0.499	0.190	1.311
Brainstem	0.566	0.735	0.256	2.107	0.684	0.850	0.390	1.854
Spinal cord	0.678	0.704	0.134	3.685	0.852	1.107	0.381	3.218
Optic nerve	0.269	2.598	0.477	14.138	0.490	1.748	0.358	8.524
Cerebrum	0.529	0.715	0.251	2.033	0.987	1.006	0.472	2.146
Histologic subtype								
Pilocytic astrocytoma	1	Ref	Ref	Ref	1	Ref	Ref	Ref
Anaplastic glioma	0.000	7.842	3.197	19.235	0.000	17.425	9.303	32.639
Diffuse astrocytoma	0.605	1.489	0.330	6.723	0.140	2.278	0.763	6.797
Glioblastoma	0.000	36.502	18.340	72.651	0.000	55.716	31.806	97.597
Oligodendroglioma	0.007	3.769	1.442	9.849	0.014	2.997	1.244	7.219

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Table 3. Continued

	Death within 1 Month				Death within 3 Months			
			95% CI				95% CI	
Characteristics	*P* Value	OR	Low CI	High CI	*P* Value	OR	Low CI	High CI
Extent of resection								
Biopsy	1	Ref	Ref	Ref	1	Ref	Ref	Ref
Subtotal resection	0.366	0.716	0.348	1.477	0.519	1.192	0.699	2.030
Gross total resection	0.018	0.401	0.188	0.856	0.005	0.410	0.219	0.769
Unknown	0.062	0.237	0.053	1.072	0.429	0.710	0.304	1.660
Radiation								
No	1	Ref	Ref	Ref	1	Ref	Ref	Ref
Yes	0.000	0.026	0.003	0.190	0.000	0.124	0.065	0.237
Chemotherapy								
No	1	Ref	Ref	Ref	1	Ref	Ref	Ref
Yes	0.000	0.073	0.028	0.190	0.000	0.162	0.098	0.267

OR, odds ratio; CI, confidence interval.

pediatric glioma. However, some limitations in the presented study should be considered. On the one hand, the SEER database did not capture the genetic information, such as DH1, and BRAF, which also impacted the prognosis of pediatric glioma. As a result, we could not include those molecules into the analysis. On another hand, the SEER dataset lacked the information of schedules and doses of chemotherapy of patients received, which made it difficult to assess the exact regimens used. Further prospective studies should be conducted to confirm and extend our results.

In conclusion, we found a decrease in early mortality during the past 40 years. The death rates within 1 month and 3 months after diagnosis were 1.32% and 2.44%, respectively. Glioblastoma, anaplastic glioma, and oligodendroglioma were risk factors of early mortality for children diagnosed with glioma, whereas advanced age, gross total resection, radiation, and chemotherapy were associated with low early mortality. A better understanding of the relationship between cancer-related factors and early mortality may provide insight into the therapeutic strategies for pediatric glioma with a high risk of early mortality.

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Table 3.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Xingwang Zhou: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing - original draft, Supervision, Software, Validation, Writing - review & editing. **XiaoDong Niu:** Investigation, Data curation, Formal analysis, Writing - original draft, Supervision, Writing - review & editing. **Kaijun Sun:** Visualization, Investigation. **Junhong Li:** Data curation, Formal analysis, Writing - original draft, Visualization, Investigation. **Qing Mao:** Software, Validation. **Yanhui Liu:** Conceptualization, Methodology, Writing - review & editing.

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