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Prognostic Factors and Survival Prediction of Pediatric Glioblastomas: A Population-Based Study

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ABSTRACT

AIM: To identify the risk factors for pediatric glioblastomas (GBMs), and to develop an effective prediction model to estimate the survival rate for these patients.

MATERIAL and METHODS: Pediatric patients with GBM were extracted from the Surveillance, Epidemiology, and End Results database. Kaplan-Meier analyses were performed for overall survival. Significant prognostic factors were identified using univariate and multivariate Cox regression analyses. A nomogram model was also established.

RESULTS: A total of 378 pediatric patients with GBM were included in our study. The multivariate Cox analysis revealed that age at diagnosis (HR, 1.67; 95% CI, 1.19-2.35; p=0.003), tumor site (infratentorial vs. supratentorial: HR, 1.44; 95% CI, 1.03-2.03; p=0.035), surgery (gross total resection [GTR] vs. no surgery: HR, 0.53; 95% CI, 0.36-0.77, p<0.001), and chemotherapy (HR, 0.56; 95% CI, 0.42-0.74; p<0.001) were independent prognostic factors of overall survival for pediatric GBMs. Additionally, we found that patients with tumors located in the infratentorial region (p<0.001) tended to receive conservative treatments. Moreover, our nomogram model showed favorable discriminative ability.

CONCLUSION: At the population level, we found that older children and tumors located in the infratentorial region were associated with poor survival, while both GTR and chemotherapy were associated with improved survival. There was no association between radiotherapy and survival outcomes. Moreover, a nomogram with good performance was constructed to predict the overall survival of these patients.

KEYWORDS: SEER, Pediatric glioblastoma, Prognostic factor, Nomogram

INTRODUCTION

Glioblastomas (GBMs) are the most common and aggressive type of brain tumor. Due to its highly malignant nature, the World Health Organization (WHO) classified it as grade IV. GBMs account for 15.4% of primary brain tumors and 45.6% of primary malignant brain tumors. The incidence of GBM increases with age, gradually increasing from 0.15 per 100000 (0-19 years old) to 15.03 per 100000 (75-84 years old) (12). Many studies have reported that GBMs have a bleak prognosis (1,5,12). The 5-year survival rate of patients with GBM is only 0-5% (12). Although the application of TMZ has improved patients' prognoses since 2005, the overall survival of these patients remains poor.

Currently, most studies focus on adult GBM rather than pediatric patients. Due to the absence of related studies, the clinical characteristics and prognostic factors of pediatric patients with GBM remain poorly defined. The Central Brain Tumor Registry of the United States reported that GBMs comprised approximately 3% of all primary brain and central nervous system tumors in children (12). Given its rarity, most studies on GBMs in children are single-center studies with small samples. It is necessary to use population-based data

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to identify the clinical characteristics and prognostic factors of pediatric patients with GBMs.

Moreover, considering the poor prognosis of GBMs and the difficulty in predicting survival for individual patients, a more precise prognostic tool is needed to estimate survival for these patients in order to aid clinical decisions and optimize their treatments. Therefore, we also established a nomogram for reliable prediction of the 1-, 3-, and 5-year overall survival (OS) values in our study.

MATERIAL and METHODS

Data Selection from the SEER Database

The Surveillance, Epidemiology, and End Results (SEER) database contains information on the demographics, treatment, and survival of cancer patients. We used the SEER database for our analysis. The selection criteria included: 1) patients who were diagnosed with GBM as defined by the International Classification of Diseases for Oncology Third Edition (ICD-O–3) histology code (9440/3) and site code (C71.0-C71.9); 2) pediatric patients (<18 years old) who were diagnosed between 2000 and 2015; 3) patients who were being treated for GBM as their only or first malignancy, and 4) patients who had complete follow-ups. Patients diagnosed by autopsy or without a histologically confirmed diagnosis were excluded from our study.

Definitions of the Variables and Endpoint

The clinicopathologic variables extracted for our analysis included patients' year of diagnosis (2000-2004 or 2005-2015), age at diagnosis (≤5 or 6-17), sex (male or female), race (white, black, or other), primary site of their GBM (supratentorial, infratentorial, NOS), tumor size (<50 mm or ≥50 mm), surgery type (no surgery, partial resection, gross total resection [GTR]), radiotherapy (yes or no), and chemotherapy (yes or no). OS was used as the endpoint.

Statistical Analyses

First, our study summarized the patient demographics and clinical characteristics using numbers and percentages. Second, univariate and multivariate analyses using the Cox proportional hazards model were employed to test the prognostic factors of OS. The Kaplan-Meier method, Student's *t*-test, and Chi-square test were conducted where appropriate. Lastly, a nomogram model was developed to estimate the OS for GBMs based on the results from the Cox analyses. The concordance index (C-index) and receiver operating characteristic curve (ROC) with the area under the ROC curve (AUC) values were applied to evaluate the discriminative ability of the nomogram model. Decision curve analyses (DCA) were used to evaluate the clinical usefulness and benefits of the prediction model. Bootstrap analyses with 1,000 resamples were conducted for these analyses. $p<0.05$ was considered statistically significant. All statistical analyses were performed using R version 3.2.3 software.

RESULTS

Demographics and Characteristics of Patients

A total of 378 pediatric patients with GBM were identified between 2000 and 2015. The patient characteristics are summarized in Table I. About three-quarters of the patients were diagnosed after 2005. A total of 26.5% of patients diagnosed with GBM before the age of 5, and others (73.5%) were diagnosed during the ages of 6-17. The male-to-female

Table I: Patient Demographics

Characteristic	n (%)
Total	378 (100)
Year of diagnosis	
2000-2004	98 (25.9)
2005-2015	280 (74.1)
Age at diagnosis (years)	
≤5	100 (26.5)
6-17	278 (73.5)
Gender	
Male	213 (56.3)
Female	165 (43.7)
Race	
White	273 (72.2)
Black	61 (16.1)
Others	44 (11.6)
Tumor site	
Supratentorial	240 (63.5)
Infratentorial	73 (19.3)
NOS	65 (17.2)
Tumor size	
<50 mm	150 (39.7)
≥50 mm	136 (36.0)
Unknown	92 (24.3)
Surgery type	
No surgery	69 (18.3)
STR	190 (50.3)
GTR	119 (31.5)
Radiation	
No	96 (25.4)
Yes	282 (74.6)
Chemotherapy	
No	108 (28.6)
Yes	270 (71.4)

STR: *Subtotal resection,* ***GTR:*** *Gross total resection.*

ratio was approximately 1.3. The majority of patients were white (72.2%) and black (16.1%). Regarding tumor characteristics, 63.5% of neoplasms were located in the supratentorial region and 19.3% were located in the infratentorial region. Surgery is the primary treatment for GBM, and only 69 patients (18.3%) in our cohort had not undergone surgery. Among the patients who underwent surgery, 190 underwent STR and 119 underwent GTR. The vast majority of patients received adjuvant therapy, 282 patients (74.6%) were treated with radiation, and 270 (71.4%) were treated with chemotherapy.

Independent Prognostic Factors of OS

As shown in Table II, the univariate survival analysis found that increasing age at diagnosis (HR, 1.59; 95%CI, 1.19-2.11; p=0.002) and tumors located in the infratentorial region (HR, 1.55; 95%CI, 1.17-2.07; p=0.003) were significantly associated with lower OS. Patients who received surgery treatment had a better prognosis, either STR (HR, 0.67; 95%CI, 0.50-0.90; p=0.008) or GTR (HR, 0.43; 95%CI, 0.31-0.60; p<0.001), compared with those who did not. Additionally, adjuvant chemotherapy (HR, 0.48; 95%CI, 0.38-0.62; p<0.001) was also associated with improved survival.

Table II: Univariate and Multivariable Cox Regression Analyses

	Univariate		Multivariate	
Characteristic	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Year of diagnosis	1.00 (0.98-1.03)	0.879	1.01 (0.98-1.04)	0.517
Age at diagnosis (years)				
≤ 5	1[Reference]		1[Reference]	
6-17	1.59 (1.19-2.11)	**0.002**	1.67 (1.19-2.35)	**0.003**
Gender				
Male	1[Reference]		1[Reference]	
Female	0.97 (0.77-1.22)	0.815	0.89 (0.70-1.12)	0.322
Race				
White	1[Reference]		1[Reference]	
Black	1.12 (0.82-1.53)	0.476	1.02 (0.74-1.41)	0.889
Others	0.69 (0.48-1.01)	0.056	0.63 (0.43-0.93)	0.019
Tumor site				
Supratentorial	1[Reference]		1[Reference]	
Infratentorial	1.55 (1.17-2.07)	**0.003**	1.44 (1.03-2.03)	**0.035**
NOS	0.84 (0.60-1.17)	0.302	0.82 (0.59-1.16)	0.265
Tumor size				
< 50 mm	1[Reference]		1[Reference]	
≥ 50 mm	0.89 (0.68-1.15)	0.368	1.23 (0.92-1.65)	0.161
Unknown	1.07 (0.80-1.44)	0.637	1.39 (1.02-1.91)	0.038
Surgery type				
No surgery	1[Reference]		1[Reference]	
STR	0.67 (0.50-0.90)	**0.008**	0.78 (0.56-1.09)	0.143
GTR	0.43 (0.31-0.60)	**<0.001**	0.53 (0.36-0.77)	**0.001**
Radiation				
No	1[Reference]		1[Reference]	
Yes	1.06 (0.81-1.40)	0.675	0.89 (0.62-1.28)	0.531
Chemotherapy				
No	1[Reference]		1[Reference]	
Yes	0.48 (0.38-0.62)	**<0.001**	0.56 (0.42-0.74)	**<0.001**

STR: *Subtotal resection,* ***GTR:*** *Gross total resection.*

After adjusting for available clinical factors using multivariate Cox analyses, we found that GTR (HR, 0.53; 95%CI, 0.36-0.77; p<0.001), and chemotherapy (HR, 0.56; 95%CI, 0.42-0.74; p<0.001) were identified as independent protective predictors, whereas older ages in children (HR, 1.67; 95%CI, 1.19-2.35; p=0.003) and tumors located in the infratentorial region (HR, 1.44; 95%CI, 1.03-2.03; p=0.035) were associated with poor survival. Remarkably, radiation was not significantly associated with prognosis in pediatric GBMs. Furthermore, our study found no significant improvements in survival from 2000 to 2015.

Patients who were diagnosed after 2005 had no significant improvements in survival compared with patients diagnosed before 2005 (p=0.65, Figure 1A). Although this may be due to our small sample size, it illustrates the need for intensive study of pediatric GBMs. Moreover, the Kaplan-Meier analysis with log-rank tests also indicated that patients under 5 years of age had a significantly better OS than those aged 6-17 years (p=0.0011, Figure 1B). Tumors located in the supratentorial region had significantly better OS than those located in the infratentorial region (p=0.0016, Figure 1C). In order to analyze further the underlying causes of survival differences, we conducted a comparative analysis of the demographic and treatment factors according to patient age and tumor location. As shown in Tables III and IV, older children (p<0.001) and tumors located in the infratentorial region (p=0.019) tended to receive radiation treatment. Patients with tumors located in the infratentorial region were more likely to receive conservative treatments (p<0.001). Compared with tumors located in the supratentorial region, tumors located in the infratentorial region were smaller (p<0.001).

Construction and Validation of the Predictive Model

The results from the multivariate Cox analyses were visualized in the shape of a nomogram model to help estimate the 1-, 3-, and 5-year survival for pediatric GBMs (Figure 2). The C-index was 0.701 for the nomogram model, which indicated a favorable discriminative ability. The calibration curves showed good consistency between the predictions and observations (Figure 3A). The AUCs were 0.70, 0.76, and 0.77 for the 1-year, 3-year, and 5-year predicted OS values, respectively (Figure 3B). These results indicate that our nomogram model has

Table III: Comparison of Demographic and Treatment Factors by Patient Age

	≤5, n (%)	6-17, n (%)	p
Gender			0.135
Male	50 (50)	163 (58.6)	
Female	50 (50)	115 (41.4)	
Race			0.268
White	66 (66.0)	207 (74.5)	
Black	20 (20.0)	41 (14.7)	
Others	14 (14.0)	30 (10.8)	
Tumor site			0.183
Supratentorial	54 (71.1)	186 (78.5)	
Infratentorial	22 (28.9)	51 (21.5)	
Tumor size			0.54
<50 mm	35 (49.3)	115 (53.5)	
≥50 mm	36 (50.7)	100 (46.5)	
Surgery type			0.828
No surgery	20 (20.0)	49 (17.6)	
STR	48 (48.0)	142 (51.1)	
GTR	32 (32.0)	87 (31.3)	
Radiation			**<0.001**
No	59 (59.0)	37 (13.3)	
Yes	41 (41.0)	241 (86.7)	
Chemotherapy			0.161
No	34 (34.0)	74 (26.6)	
Yes	66 (66.0)	204 (73.4)	

STR: *Subtotal resection,* ***GTR:*** *Gross total resection.*

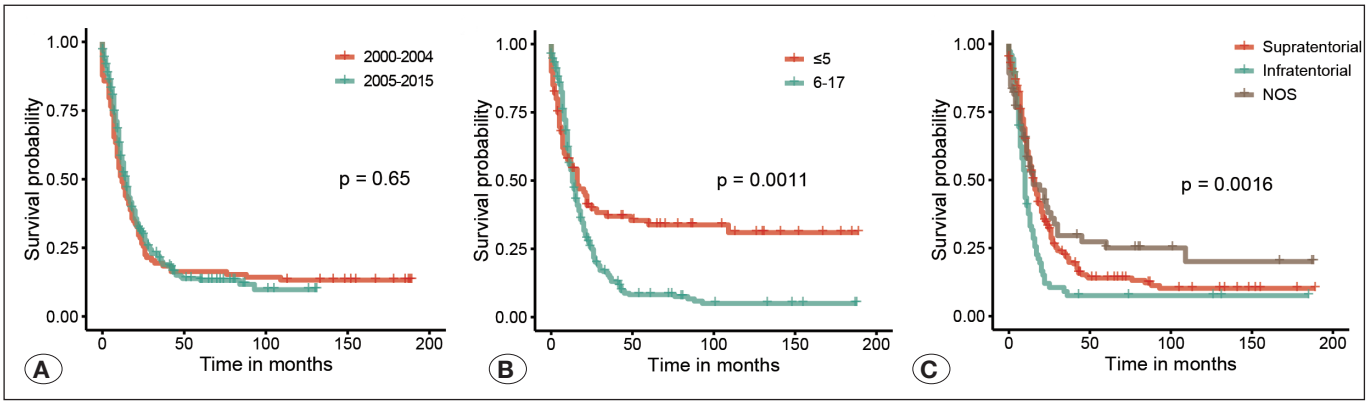

Figure 1: Kaplan-Meier curves with log-rank tests for patients with GBM. **A)** Year of diagnosis; **B)** age of diagnosis; **C)** tumor location.

favorable prediction abilities. DCA was conducted to verify the clinical usability and benefits of the nomogram. As shown in Figure 3C, the nomogram's DCA curves exhibited larger net benefits across a range of death risks.

DISCUSSION

GBM is the most common malignant primary intracranial neoplasm, mainly diagnosed at an older age, with a mean age of 55 years at diagnosis (7). It is rare in children. Therefore, adult GBM treatment strategies are well established and comprehensive; these include surgical resection, radiation, and TMZ chemotherapy (13). Immunotherapy is also being gradually applied in clinics. Due to its rarity, there is little research on pediatric GBMs. There seems to be a unique pediatric group with GBMs. However, clinical trials for pediatric GBMs are normally based on previously tested and often ineffective treatments without consideration of the differences

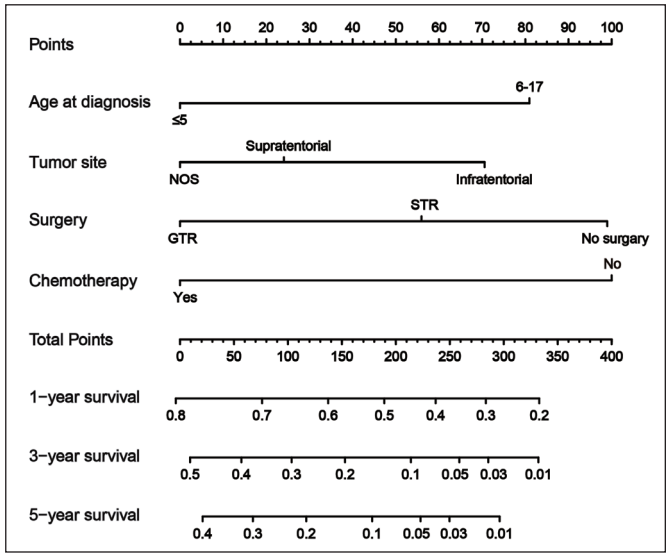

Figure 2: Nomogram for predicting 1-, 3-, 5-year OS in pediatric GBM patients.

Table IV: Comparison of Demographic and Treatment Factors by Tumor Site

	Supratentorial	Infratentorial	p
Age at diagnosis (years)	9.87+5.19	8.32+4.49	0.061
	n (%)	**n (%)**	
Gender			0.223
Male	141 (58.8)	37 (50.7)	
Female	99 (41.3)	36 (49.3)	
Race			0.586
White	172 (71.7)	51 (69.9)	
Black	42 (17.5)	11 (15.1)	
Others	26 (10.8)	11 (15.1)	
Tumor size			<0.001
<50 mm	81 (42.9)	53 (93.0)	
≥50 mm	108 (57.1)	4 (7.0)	
Surgery type			<0.001
No surgery	29 (12.1)	30 (41.1)	
STR	125 (52.1)	34 (46.6)	
GTR	86 (35.8)	9 (12.3)	
Radiation			**0.019**
No	61 (25.4)	9 (12.3)	
Yes	179 (74.6)	64 (87.7)	
Chemotherapy			0.304
No	61 (25.4)	23 (31.5)	
Yes	179 (74.6)	50 (68.5)	

STR: *Subtotal resection,* ***GTR:*** *Gross total resection.*

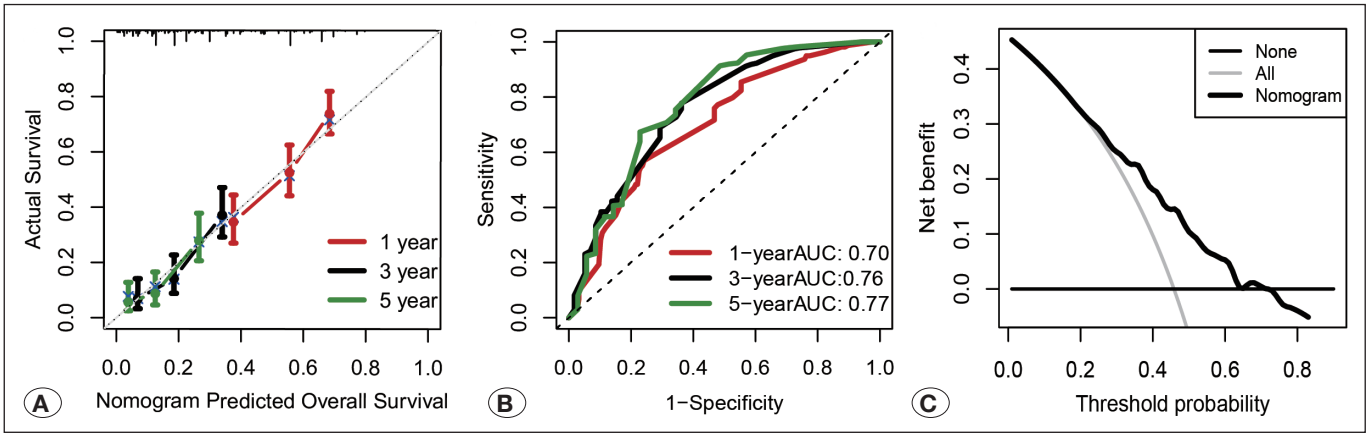

Figure 3: Calibration curves of the nomogram for predicting OS in GBM patients **(A)**; the AUC of ROC curves for 1-, 3-, 5-year OS **(B)**; Decision curve analysis for 1-, 3-, 5-year OS **(C)**.

between neoplasms in adults and children. Prognostic factors related to pediatric GBMs are still being explored. It is necessary to call attention to pediatric GBMs in order to improve tumor management methods and patient survival. In addition, nationwide datasets have been advocated for the clinical evaluation of rare diseases such as pediatric GBMs (17). Therefore, using the SEER database, our research focused on the demographic and clinical characteristics of pediatric GBMs in order to explore statistically significant prognostic factors and establish a prediction model to predict the survival of a single individual.

By analyzing the data on pediatric GBMs, our study found that increasing age at diagnosis and tumors located in the infratentorial region were associated with poor survival. Patients who received GTR and were treated with chemotherapy had increased survival. Older children and neoplasms located in the infratentorial region tended to receive radiation treatment. Moreover, patients with tumors located in the infratentorial region were more likely to be treated without surgical resections. The survival of patients has not been significantly optimized since 2000.

Our study found that younger ages were significantly related to increased survival. Similar findings were also noted by other researchers (8,16,18). Lam et al. reported patients under 5 years of age with a 5-year cause-specific survival of 40% and 54% for patients under 1 year of age (8). Conversely, Nikitović et al. (11), and Perkins et al. (15) found no association between age at diagnosis and survival, which may be attributed to their small sample size. To explore the causes of different prognoses for patients of different ages, we further performed a contrast analysis of the demographic and treatment factors according to age at diagnosis. We found that older children were more likely to receive radiation therapy, which may be related to the claim that children under 3 years of age should avoid radiotherapy to reduce long-term neurological sequelae (6,15). However, radiotherapy was not found to be related to patient outcomes, and it could not account for the different survival rates of the various age groups. In recent years, differences in DNA copy numbers and gene expression between pediatric and adult GBMs were found, especially for somatic histone mutations (2,14). This may explain the discrepant results in the different age groups to some extent.

Our study also found that tumors located in the infratentorial region (brain stem and cerebellum) were associated with tragic survival rates. The results of many studies are in line with ours (8,10). MacDonald et al. reported that tumors located in the pontine region were related to the poorest outcomes (10). Moreover, in the study by Lam et al., tumor location was a significant prognostic factor (8). After more analysis, we found that the infratentorial GBMs tended to receive STR or conservative treatments compared to supratentorial GBMs. Surgery is fundamental for treating GBMs. The multivariate Cox analyses in our study also revealed that GTR could significantly improve the survival prognosis of GBM patients. Infratentorial tumors are often difficult to remove completely due to their depth. This may be the reason for the differences in prognosis.

In this cohort, 75% of the patients received radiation therapy. Only 41% of patients under 5 years of age received radiotherapy, and 86.7% of patients over 5 years of age received radiotherapy. Radiotherapy is widely used in the treatment of adult GBMs. Especially after the famous Stupp trial in 2005, radiation with concomitant and adjuvant TMZ has become the gold standard treatment for GBM patients (16). However, our study found that radiotherapy did not improve the OS of pediatric patients. The survival of patients diagnosed after 2005 did not improve significantly compared to patients before 2005. We can guess that the Stupp trial did not replicate the previous successes in the treatment of pediatric patients. The results of Perkins et al. (15), Das et al. (5), and Lam et al. (8) were consistent with ours. In their study, there was no significant correlation between radiotherapy and survival. Jacola et al. exposed that pediatric patients treated with radiation therapy resulted in changes in cerebral white matter that are related to neurocognitive late effects (6). Due to the lack of detailed data on radiotherapy in the SEER database, such as the doses, timing, and volumes used, we cannot conclude that radiotherapy is not effective for children. It is possible that there was a sub-queue that could benefit from radiotherapy.

Our multivariate Cox regression analysis showed that patients who received chemotherapy had a better OS than patients who did not receive chemotherapy. Many articles have mentioned that TMZ, bevacizumab, and irinotecanas were effective treatments for GBMs (3,9,19,21). However, the Children's Oncology Group found that radiotherapy combined with TMZ had no significant effect on pediatric patients' overall survival (4). Chemotherapy still plays a major role in the treatment of pediatric GBMs.

As a novel clinical prediction tool, nomograms have been commonly used to predict survival in adult GBMs (20,22). As far as we know, no one has established a nomogram prediction model for pediatric GBMs. Based on the data from the SEER database, a nomogram was built to predict the 1-, 3-, and 5-year OSs for pediatric GBMs. Furthermore, the AUC values and C-indices also illustrate the favorable discrimination and clinical application value of the model.

We acknowledge that our research has certain limitations. First, our study was a retrospective study with an unavoidable selection bias. Second, information on the dose and type of radiotherapy and the chemotherapy regimen was not available in the SEER database. Similarly, data on genetic information, clinical symptoms, and comorbidities are not known. Finally, the nomogram just conducted an internal validation; therefore, external validations are still necessary.

CONCLUSION

In summary, by analyzing the SEER database, we found that older children and tumors located in the infratentorial region were associated with poor survival, while both GTR and chemotherapy were related to improved survival. The survival outcomes of these patients did not improve significantly after 2005. Moreover, this is the first study to establish a nomogram model with good performance in predicting overall survival in pediatric GBM patients.

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