A Risk Stratification Model Based on a Population Analysis for Predicting Cancer Specific Survival in Pediatric Brain Stem Glioma.

Kai Sun[1], Xiaowei Fei[2], Mingwei Xu[3], Wenjin Chen[4], and Ruxiang Xu[1]

[1]Sichuan Academy of Medical Sciences and Sichuan People's Hospital
[2]Fourth Military Medical University
[3]Third Military Medical University Daping Hospital and Research Institute of Surgery
[4]University of Electronic Science and Technology of China Sichuan Provincial People's Hospital

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Abstract

Introduction: The aim of this study was to construct and validate a nomogram and risk stratification model for predicting cancer-specific survival (CSS) of pediatric brainstem glioma patients. Methods: Cases of pediatric brainstem glioma patients (<12 years) from 1998 to 2016 were retrieved from the Surveillance, Epidemiology, and End Results (SEER) database and demographic, clinicopathologic characteristics, treatments, and survival outcomes were analyzed. The total cohort was randomly divided into training and validation sets, followed by univariate and multivariate Cox regression analyses. A nomogram was constructed and risk stratification analysis incorporated using the selected variables from the multivariate analysis. The accuracy of the model was assessed using C-index and calibration curves. Results: A total of 806 pediatric cases with histologically confirmed diagnosis of brainstem glioma were selected and analyzed. Multivariate analysis showed that age, race, tumor size, grade and radiotherapy (P<0.05) were independent prognostic indicators of pediatric gliomas. For prediction of CSS, the C-index of the nomogram was 0.75, which shows a good predictive probability. Conclusion: The nomogram developed in this study for predicting survival of pediatric patients with histologically confirmed stem gliomas is the first to incorporate risk stratification. Combining nomogram and risk stratification system is a convenient tool to aid clinicians in the identification of high-risk patients and to perform targeted adjuvant treatment.

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Kai Sun[1,2], Xiaowei Fei[3], Mingwei Xu[2], Wenjin Chen[1], Ruxiang Xu[1]

[1]Department of Neurosurgery, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu, Sichuan, 610072, People's Republic of China;

[2]Department of Neurosurgery, The Third Affiliated Hospital of The Third Military Medical University, Chongqing 400042, People's Republic of China;

[3]Department of Neurosurgery, The First Affiliated Hospital of The Fourth Military Medical University, Xi'an, Shaan Xi, 710032, People's Republic of China;

Correspondence

Department of Neurosurgery, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu, Sichuan, 610072,

People's Republic of China.

Tel +86 13391788118

Email: 1192217050@qq.com

Authors' contributions

(I) Conception and design: Kai Sun, Ruxiang Xu; (II) Administrative support: Kai Sun; (III) Provision of study materials or patients: Ruxiang Xu; Mingwei Xu; (IV) Collection and assembly of data: Xiaowei Fei, Wenjin Chen; (V) Data analysis and interpretation: Kai Sun; Xiaowei Fei, Ruxiang Xu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Ethics approval and consent to participate

All analyses of human data conducted in this study were approved by the Institutional Review Board of the University of Electronic Science and Technology of China and in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All authors signed authorization forms and received permission from SEER to access and use the dataset.

Consent for publication

Not applicable

Availability of data and materials

The dataset from SEER database generated and/or analyzed during the current study are available in the SEER dataset repository (*https://seer.cancer.gov/data/*).

Competing interests

The authors declare that they have no competing interests.

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(I) Conception and design: Kai Sun, Ruxiang Xu; (II) Administrative support: Kai Sun; (III) Provision of study materials or patients: Ruxiang Xu; Mingwei Xu; (IV) Collection and assembly of data: Xiaowei Fei, Wenjin Chen; (V) Data analysis and interpretation: Kai Sun; Xiaowei Fei, Ruxiang Xu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Conflicts of interest

The authors have no disclosures or conflicts of interest to declare.

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The authors acknowledge the efforts of the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries for development and maintenance of the SEER database. The authors report no conflicts of interest.

Abbreviations Table

CSS cancer-specific survival

SEER Surveillance, Epidemiology, and End Results

CNS central nervous system

DPIG diffuse intrinsic pontine gliomas

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Abstract

Background: The aim of this study was to construct and validate a nomogram and risk stratification model for predicting cancer-specific survival (CSS) of pediatric brainstem glioma patients.

Methods: Cases of pediatric brainstem glioma patients (<12 years) from 1998 to 2016 were retrieved from the Surveillance, Epidemiology, and End Results (SEER) database and demographic, clinicopathologic characteristics, treatments, and survival outcomes were analyzed. The total cohort was randomly divided into training and validation sets, followed by univariate and multivariate Cox regression analyses. A nomogram was constructed and risk stratification analysis incorporated using the selected variables from the multivariate analysis. The accuracy of the model was assessed using C-index and calibration curves.

Results: A total of 806 pediatric cases with histologically confirmed diagnosis of brainstem glioma were selected and analyzed. Multivariate analysis showed that age, race, tumor size, grade and radiotherapy (P<0.05) were independent prognostic indicators of pediatric gliomas. For prediction of CSS, the C-index of the nomogram was 0.75, which shows a good predictive probability.

Conclusion: The nomogram developed in this study for predicting survival of pediatric patients with histologically confirmed stem gliomas is the first to incorporate risk stratification. Combining nomogram and risk stratification system is a convenient tool to aid clinicians in the identification of high-risk patients and to perform targeted adjuvant treatment.

Keywords: Glioma, Nomogram, Prognosis, Brainstem, SEER

Background

Gliomas constitute a wide spectrum of neuroepithelial tumors arising from glia or supporting cells (astrocytes, oligodendrocytes, and ependymocytes) of the central nervous system (CNS)[1,2]. Gliomas are responsible for nearly 24% of all primary brain and CNS neoplasms and vastly differ in histology and behavior ranging from benign ependymomal tumors to the most aggressive and lethal grade IV glioblastoma multiforme[3]. Specifically, brainstem gliomas are diverse groups of neoplasms that primarily affect children and include low-grade focal brainstem gliomas, as well as high-grade diffuse intrinsic pontine gliomas (DIPG)[4,5]. Although 80% of gliomas arise within the pons as DIPGs, the remaining low-grade gliomas are located within the midbrain, dorsal medulla, or the cervico-medullary junction. The aforementioned locations of these neoplasms pose therapeutic challenges, and hence, may negatively affect treatment outcomes.

Radiotherapy, chemotherapy, or combined treatment modalities are the standard therapeutic options for gliomas[6]. Previous studies have reported failure of chemotherapy in treating DIPGs due to the lack of intratumor penetration[7,8]. Recently, the unraveling of the genetic landscape of DIPGs together with identification of the K27M mutation (mutation in both histones H3.1 and H3.3) has improved the understanding of the pathogenesis of gliomas and identification of novel targeted therapies[9,10].

Despite a wealth of information on cancer staging, prediction of survival and treatment strategies, little is known about the determinants of cancer-specific survival in childhood brain stem glioma. The Surveillance, Epidemiology, and End Results (SEER) database of survival data from population-based cancer registries encompass ˜28% of the American population[11,12]. The aim of the current study was to characterize a comprehensive, accurate and useful prognostic model using a population-based SEER analysis to predict survival of pediatric cases of stem gliomas.

Material and Methods

Ethical approval

This is a population study with anonymized data and was therefore exempt from ethics declaration because the study was deemed not to constitute human subject research.

Study Design and Patients Selection

This population study used SEER-18 Dataset comprised 18 cancer registries across the United States. Pediatric (<12 years) patients with histologically confirmed glioma diagnosed between 1998 and 2016 were included in this study. Patient data with incomplete clinical data of interest and therapy details, and poor follow up were excluded. Further, cases wherein the primary site of lesion was not brainstem were also excluded (Figure 1). Data were extracted using the SEER*Stat software (version 8.3.5) of the National Cancer Institute. Clinical characteristics retrieved in the study were prospective data on patient demographics, tumor characteristics, and survival outcomes.

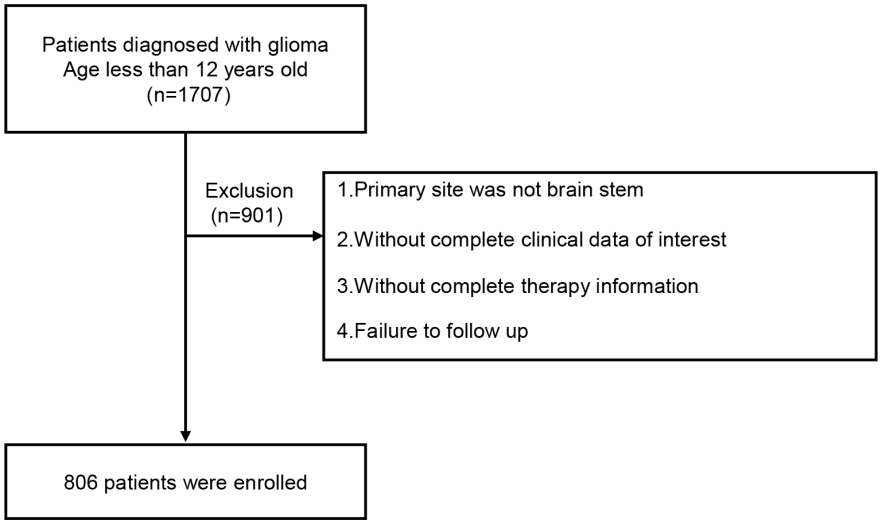

Figure 1: Patient selection of pediatric patients with brainstem gliomas within the SEER database.

SEER Coding and Variable Definitions

Demographic data included age at diagnosis, gender, and race; the latter was categorized into White/Caucasian, Black/African American and other. Tumor characteristics included histologic grade, stage, and size. Based on the study population's median value of largest tumor dimension in any direction, tumors were categorized into large (>3 cm), small ([?]3 cm), and of unknown size. Data on treatment course including surgical resection - other than biopsy, radiation therapy, and chemotherapy were retrieved from the SEER database. The era of diagnosis divided in 10-year intervals (1998-2008 and 2009-2016) was also introduced as a covariate variable.

Statistical Methods

The chi-squared test was used to compare continuous variables (rates) and categorical variables (histological grades and stage of gliomas). Kaplan–Meier plots were used for the determining the survival difference of variables. Cox regression was used for identifying risk factors of prognosis and included univariate and multivariate analyses Clinically important variables that showed significance ($P<0.1$) in the univariate analysis formed the input for multivariate analysis using the Cox risk regression model with backward elimination. Variables that showed significance ($P<0.0001$) in the multivariate analysis were selected for developing a nomogram. CSS was determined for 1, 3 and 5-years. Accuracy of the nomogram was assessed using C-index and calibration curves generated following 1000 bootstrap resampling. A decision curve analysis is a net benefit analysis that compares the true-positive to the weighted false-positive rates across different risk thresholds that a clinician/patient might want to accept. Based on the median value of the total scores in the

nomogram, a risk stratification model was built and comprised patients who were divided into two prognostic groups. All statistical analyses were performed using R and Empower Stats [www.empowerstats.com, XY Solutions, Inc. Boston MA]. A two-tailed P value <0.05 was considered statistically significant.

Results

Patient characteristics

The demographics, and clinicopathological characteristics of the patients are summarized in Table 1. A total of 1707 patients were screened, of which 901 were excluded (figure 1). Finally, 806 pediatric cases with histologically confirmed diagnosis of brainstem glioma were selected and analyzed. The median patient age at diagnosis was 6 years (range, 0-12). Patients were predominantly White (n= 596, 74%), followed by Black/African American (n=138, 17.1%) and other ethnic groups (n= 72, 8.9%). Males (n= 389, 48.3%) and females (n= 417, 51.7%) were approximately equally distributed.

Of the 806 cases, tumor size of 87(10.8%) was considered small (<=3cm) and that of 265 (32.9%) were large (>3cm), and size was unknown for 454 (56.3%). The histological grade of most tumors was unknown (n = 739; 91.7%). Most tumors (n = 720; 89.3%) were historic localized stage. Regarding treatment radiation therapy was the most common treatment employed for glioma (n=567, 70.3%), followed by chemotherapy (n=360, 44.7%); only 25 (3.1%) underwent some form of surgical resection. The median follow-up duration was 11 months. Of the total, 566 (70%) was randomly selected and designated as the training cohort and the remaining 240 (30%) formed the internal validation cohort (Table 1).

Table 1: Patients demographics and clinicopathological characteristics of the study population

Factors	**Entire cohort (n=806)**	**Entire cohort (n=806)**	**Training cohort (n=566)**	**Training cohort (n=566)**	**Validation cohort (n=240)**	**Validation cohort (n=240)**
	N	**%**	**N**	**%**	**N**	**%**
Age at diagnosis, years	Age at diagnosis, years	Age at diagnosis, years	Age at diagnosis, years	Age at diagnosis, years	Age at diagnosis, years	Age at diagnosis, years
Median	6	6	6	6	6	6
Range	0-12	0-12	0-12	0-12	0-12	0-12
Race						
White	596	74.0	426	75.3	170	70.8
Black	138	17.1	101	17.8	37	15.4
Other	72	8.9	39	6.9	33	13.8
Sex						
Male	389	48.3	278	49.1	111	46.2
Female	417	51.7	288	50.9	129	53.8
YOD						
1998-2008	457	56.7	311	54.9	146	60.8
2009-2016	349	43.3	255	45.1	94	39.2
Tumor size, diameter, cm						
[?]3	87	10.8	54	9.5	33	13.8
¿3	265	32.9	197	34.8	68	28.3
Unknown	454	56.3	315	55.7	139	57.9
Histologic grade						
Well	10	1.24	8	1.4	2	0.8
Moderately	25	3.1	17	3	8	3.3

Factors	Entire cohort (n=806)	Entire cohort (n=806)	Training cohort (n=566)	Training cohort (n=566)	Validation cohort (n=240)	Validation cohort (n=240)
Poorly	10	1.24	7	1.24	3	1.3
Undifferentiated	22	2.73	16	2.8	6	2.5
Unknown	739	91.7	518	91.5	221	92.1
Stage						
Localized	720	89.3	506	89.4	214	89.2
Regional	76	9.4	51	9.0	25	10.4
Distant	10	1.2	9	1.6	1	0.4
Surgery						
None	781	96.9	551	97.3	230	95.8
Yes	25	3.1	15	2.7	10	4.2
Radiotherapy						
None	239	29.6	169	29.9	70	29.2
Yes	567	70.4	397	70.1	170	70.8
Chemotherapy						
None	446	55.3	310	54.8	136	56.7
Yes	360	44.7	256	45.2	104	43.3
Median Follow-up (Months)	11	11	11	11	11	11

Abbreviations: YOD, year of diagnosis

Independent prognostic factors in the training cohort

The univariate Cox-Regression analysis showed a significant association between CSS and age at diagnosis, race, sex, tumor size, histologic grade, historic stage, chemotherapy and radiotherapy. Therefore, these variables formed the input for the multivariate Cox-Regression analysis, which revealed that age, race, tumor size, grade and radiotherapy ($P<0.05$) were independent prognostic factors (Table 2).

Table 2. Univariate and multivariate analysis for the training cohort.

Factors	Univariate analysis	Univariate analysis	Univariate analysis	Multivariate analys
	HR	**95% CI**	p*	**HR**
Age at diagnosis, years				
6	1			1
¿6	0.6	0.5-0.8	<0.001	0.8
Race				
White	1			1
Black	0.9	1.0-1.2	0.037	0.8
Other	1.4	0.9-2.0	0.111	0.6
Sex				
Male	1			1
Female	1.3	1.0-1.5	0.028	1.1
YOD				
1998-2008	1			
2009-2016	0.9	0.8-1.2	0.568	
Tumor size, diameter, cm				
3	1			1

Factors	Univariate analysis	Univariate analysis	Univariate analysis	Multivariate analys
¿3	4.6	2.8-7.6	<0.001	1.9
Unknown	2.8	1.7-4.5	<0.001	1.7
Histologic grade				
Well	1			1
Moderately	0.7	0.2-3.0	0.669	0.8
Poorly	3.4	0.9-13.2	0.075	1.5
Undifferentiated	4.8	1.4-16.6	0.013	2.1
Unknown	2.1	0.7-6.7	0.189	1.3
Stage				
Localized	1			1
Regional	1.4	1.0-1.9	0.068	1.2
Distant	2.4	1.2-4.7	0.009	1.5
Surgery				
None	1			
Yes	0.6	0.3-1.2	0.164	
Radiotherapy				
None	1			1
Yes	5.9	4.3-8.2	<0.001	4.7
Chemotherapy				
None	1			1
Yes	1.8	1.5-2.3	<0.001	1.0

Abbreviations: YOD, year of diagnosis. HR, hazard ratio.

Constructing and Validating of Nomogram

Variables that were used to construct a nomogram for predicting the CSS of patients included age, race, tumor size, grade and radiotherapy (P<0.05) (Figure 2). Each of the independent factors were scored on a point scale axis (Table 2) and the total score calculated as the sum of each score was projected on the bottom scale and the probabilities of 1-, 3- and 5-year CSS for individual patients were thus estimated.

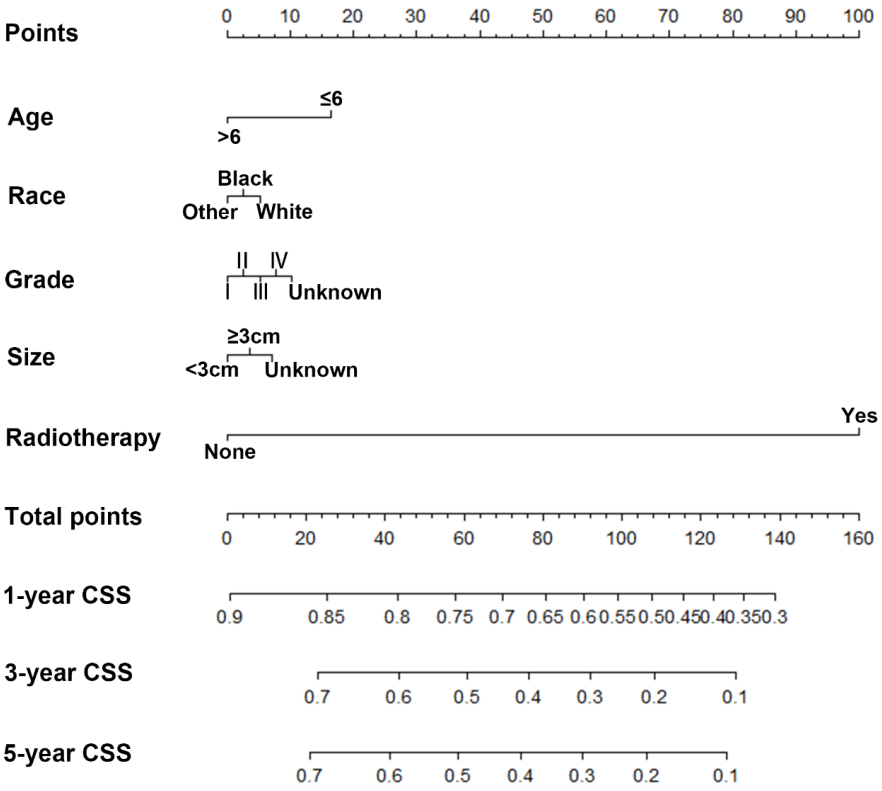

Figure 2. Nomogram predicting 1-, 3- and 5-year cancer specific survival for pediatric brainstem glioma patients.

The C-index of the nomogram thus constructed was 0.75, which demonstrates a relatively great predictive probability. Calibration plots of the nomogram (Figure 3) demonstrated an agreement between predicted CSS and the actual observations. The decision curve analysis evaluated 1,3 and 5-year CSS of children stem glioma patients, which showed all models had a better net benefit compared to the "treat all" strategy (Figure 4).

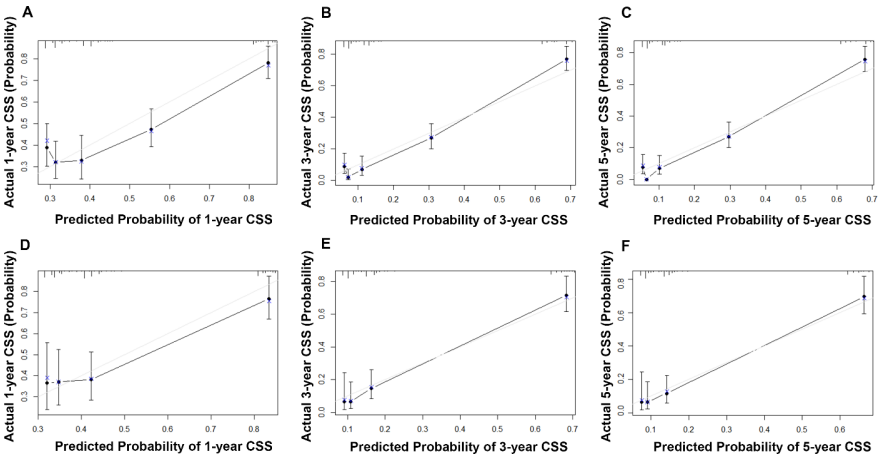

Figure 3. The calibration curves predicting 1-, 3- and 5-year cancer specific survival in the training cohort (A-C) and validation cohort (D-F).

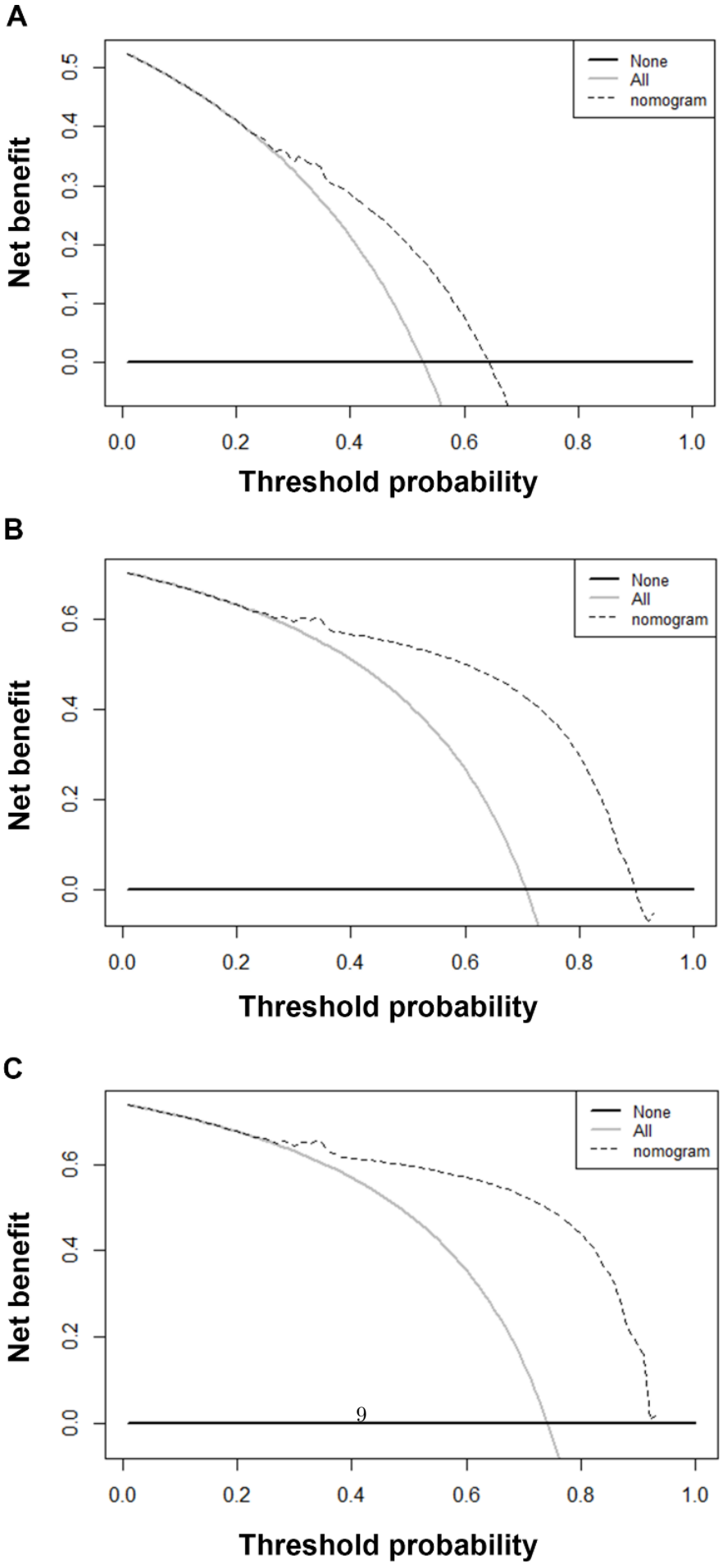

Figure 4. Decision curve analysis to show the predictive performance in 1, 3 and 5-year CSS probability (A-C). The horizontal black line represents the assumption that no patient should take the necessary measures, while the grey inverse curve represents the assumption that all patients should. The y-axis represents the net benefit, which was calculated by adding points associated with benefits and subtracting those associated with harms.

Risk stratification system

The total predicted score calculated from the nomogram was used in a risk stratification system for predicting patient survival. Patients were grouped into those with low (total score, $<$ 130.78) and high (total score, [?]130.78) risk. The median survival of the entire cohort of patients with low risk, and high risk were 24 and 7 months, respectively. It showed that Kaplan-Meier survival curves predicted by the nomogram were significantly different (Figure 5F).

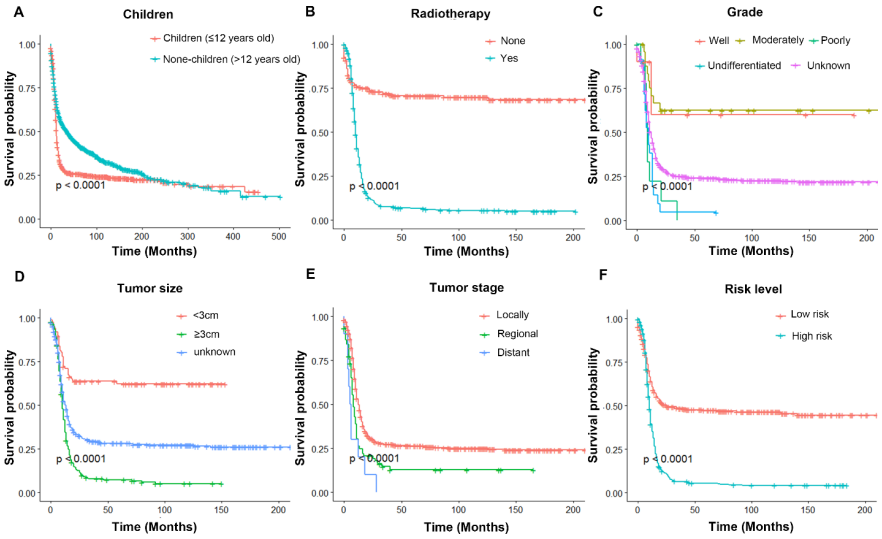

Figure 5. Kaplan-Meier curves of pediatric patients with brainstem gliomas in terms of married age (A), radiotherapy (B), historic grade (C), tumor size (D), tumor historic stage (E) and risk stratification level (F).

Discussion

As few studies have established nomogram for predicting the survival of patients with brainstem glioma patients, the sample size involved was small, and the prognostic factors have been limited[13]. Thus, we developed a clinical nomogram to predict the survival based on SEER database. The SEER registry is the largest population-based database of cancer patients in the United States, covering approximately 26% of patients diagnosed with cancer in the nation. We reviewed patients' data from the latest version of the SEER as released in 2015 (covering 18 registries, 1973-2015), by using SEER*Stat version 8.3.5, and we also set a strict inclusion and exclusion criteria.

In this study, patient survival was predicted using a clinical nomogram that was based on SEER database. This was necessitated because the traditional staging classification, which is commonly used for survival predicting and clinical strategies selecting for patients with cancers cannot accurately and consistently distinguish the difference in survival among various stages. The nomogram is a comprehensive, accurate, and useful prognostic model, which has been previously used for many kinds of malignances. However, in those studies, the limitations were small sample sizes and analysis of few prognostic factors. Five independent prognostic factors: age, race, tumor size, grade and radiotherapy, identified through univariable and multivariable Cox-Regression analyses were incorporated in the clinical nomogram. Tumor histology grade

category contributed significantly to prognosis, according to the nomogram, which is consistent, but not identical, with previous studies on survival risk factors for glioma patients, where poorly differentiated and undifferentiated status were highly associated with poor prognosis in children stem glioma patients. Most people with low-grade gliomas are treated with surgery and may receive radiotherapy thereafter. However, in this study, we found that pediatric brainstem gliomas patients had no survival benefits from radiotherapy. We also found that chemotherapy, was not an effective measure to improve outcome in cases retrieved from the SEER database[14,15]. There was a relatively significant effect of race on patient survival with longer median survival times in white people compared to black people.

For validation of the nomogram to guarantee that the model could be generally applied and to avoid overfitting, it was necessary to evaluate discrimination using the C-index and calibration, which was assessed by comparing the agreement between predicted and actual survival of patients[16,17]. Our nomogram discriminated and predicted survival more efficiently than the traditional staging system. Further, the decision curves analysis showed that our model had a better clinical net benefit across all threshold probabilities[18,19]. Moreover, the risk stratification system applied to two risk groups of patients could discriminate CSS in children stem glioma.

The strength of our analysis of the risk stratification system is that the nomogram was an accurate and reliable prognostic model that could aid clinicians identify high-risk patients for targeted adjuvant treatment, particularly for our highly selective cohort[20]. There were some certain limitations in our study. First, although we performed multivariable analysis to minimize confounder effect associated with the heterogeneities, this was a retrospective analysis, which was further compromised by the small sample size and must be accounted for when interpreting the results[21]. Second, the retrospective analysis may have introduced the possibility of selection bias in the study design[22]. Third, the SEER database lacks information on modern gene-array technology and molecular biomarkers, such as status IDH1/TERT expression[23-26], which have proven to be associated with CSS in children stem glioma patients. Therefore, future prospective analysis is warranted to predict survival of pediatric cases of gliomas.

Conclusion

The novel nomogram developed in the current study for predicting survival of pediatric patients with histologically confirmed brainstem gliomas is the first to incorporate risk stratification. Therefore, combining nomogram and risk stratification system is a convenient tool to help clinicians identify high-risk patients and to perform targeted adjuvant treatment.

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Figure Legend

Figure 1: Patient selection of pediatric patients with brainstem gliomas within the SEER database.

Figure 2. Nomogram predicting 1-, 3- and 5-year cancer specific survival for pediatric brainstem glioma patients.

Figure 3. The calibration curves predicting 1-, 3- and 5-year cancer specific survival in the training cohort (A-C) and validation cohort (D-F).

Figure 4. Decision curve analysis to show the predictive performance in 1, 3 and 5-year CSS probability (A-C). The horizontal black line represents the assumption that no patient should take the necessary measures, while the grey inverse curve represents the assumption that all patients should. The y-axis represents the net benefit, which was calculated by adding points associated with benefits and subtracting those associated with harms.

Figure 5. Kaplan-Meier curves of pediatric patients with brainstem gliomas in terms of married age (A), radiotherapy (B), historic grade (C), tumor size (D), tumor historic stage (E) and risk stratification level (F).