

Preoperative Risk-Stratification of Pediatric Malignant Brainstem Glioma based on a validated nomogram: A SEER based Analysis

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Research Article

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Abstract

Purpose: Pediatric patients diagnosed with brainstem malignant gliomas (BSMGs) have a poor prognosis. Our study aimed to construct and validate a prognostic nomogram to predict the cancer-specific survival preoperatively (CSS) rates and then a risk-stratification given to these patients.

Methods: From 1998 to 2016, we extracted patients' data from Surveillance Epidemiology and End Results (SEER) database. A total of 1160 patients were enrolled and randomly divided into training and validating groups. Subsequently, the Cox regression analysis was used to screen variables. Then, the nomogram was constructed. Lastly, we calculated C-indexes and plotted calibration curves and the utility of decision curve analyses (DCAs) to assess our survival model's benefits.

Result: Here, after multivariate cox regression analysis, we established four variables for constructing nomogram for CSS rates. Subsequently, the C-index, the area under the receiver operating characteristic curve, and calibration curves were used to confirm the nomogram's good performance. DCAs of the nomogram indicated that both groups obtained good 1-, 3-, and 5-year net benefits.

Conclusion: The nomogram model for preoperatively predicting CSS provided a convenient and practical tool to assess pediatric patients' prognosis with BSMG.

Introduction

Among solid tumors, brain tumors are one of the leading causes of mortality in children globally.(Ostrom and Gittleman et al., 2018) Studies have shown that about 10-20% of childhood central nervous system tumors are located in the brainstem(Albright and Price et al., 1983) and are associated with a dismal prognosis.(Fisher and Breiter et al., 2000) Recently, the Central Brain Tumor Registry of the United States (CBTRUS) reported that the brainstem glioma accounts for 4.2% of all gliomas.(Dolecek and Propp et al., 2012) However, the fact that brainstem glioma is insensitive to chemotherapy and radiotherapy makes non-surgical therapy invalid.(Freeman and Farmer, 1998; Hargrave and Bartels et al., 2006) Besides, their complex anatomical structure makes surgical treatment more difficult.(Sun and Xu et al., 2020) Therefore, optimal therapy for brainstem malignant glioma (BSMG) is still under investigation.

The United States National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) is a nationally representative population-based publicly available cancer database. The SEER contains more than 8 million cancer cases from 1973 to 2016, almost 28% of the United States population.(Fuchs and Kreil et al., 2002) This database records the demographic information, tumor location, pathological information, morphology, stage of diagnosis, therapy, and prognosis of millions of malignant tumors or carcinoma patients. Besides, it provides useful data for clinical research of cancer. For instance, medical nomograms use biological and clinical variables, such as tumor grade, patient age, and sex, to determine the statistical prognostic models that generate the probability of clinical events, like cancer recurrence or death, for a particular individual.(Balachandran and Gonen et al., 2015) In this study, we extracted pediatric patients' data with primary BSMG cases from the SEER database and then constructed

nomogram to preoperatively predict patient survival rate, guide clinical prognosis and treatment decisions.

Methods

We extracted patients' data from the SEER database (1975-2016), which was released in April 2019, based on the November 2018 submission using the SEER*Stat software version 8.3.8. The inclusion criteria for all enrolled cases included: primary-site codes; C71.7, brain stem; and morphology codes such as 9380/3 (Glioma, malignant), 9401/3 (Astrocytoma, anaplastic), 9440/3 (Glioblastoma, NOS), and 9451/3 (Oligodendroglioma, anaplastic). This study focused on patients who were diagnosed between 1998 and 2016 and were younger than 18 years. On the other hand, the following exclusion criteria were used: 1. Survival months were unknown; 2. Not the first tumor.

Subsequently, we extracted the following variables: age, sex, race, age/years at diagnosis, histologic type, survival months, and cause-specific mortality. Consequently, we grouped all variables into different subgroups to make data suitable for analysis using the Rstudio software and to optimize the model. These subgroups included: sex (male, female), race (white, black, and other), age at diagnosis (≤ 9 , > 9), tumor size (≤ 25 mm, >25 mm, and Unkown), and histologic type (low-grade, high-grade, and mixed), except survival months (defined as a continuous variable). We used the X-tile software to define the groups of age/years at diagnosis and tumor size. Our primary outcomes were cancer-specific survival (CSS), and all patients were randomly divided into training and validation groups at a ratio of 7:3. Then, a log-rank test was applied to assess the survival difference between these two groups. Afterward, we did a multivariable Cox and backward stepwise Cox regression analysis to pick out prognostic variables in the training group to fit the model. Thereafter, the C-index was calculated in both the training and validation groups to assess internal validation. Later on, the following packages such as; "rms", "foreign", and "survival" in RStudio software were used in building nomogram for predicting survival rates of CSS in pediatric patients with BSMGs and were over 1-, 3-, and 5-year.

Our study also applied a calibration method with bootstrapping values to demonstrate the correlation between the actual and the predicted probability, and the operation characteristic curve (ROC) of both the training and the validation groups were plotted. Lastly, the area under the receiver operating characteristic curve (AUC) was used to assess the nomogram's prediction accuracy, whereas the decision curve analyses (DCAs) were plotted to test the clinical value of the predictive models. Notably, all of the statistical analyses were performed using the RStudio software version 1.3.1093 (<http://www.rstudio.com>)

Our study protocol was approved by the Ethical Committee of the first hospital affiliated to Jinan University, and all data deposited in the SEER database are freely available to all users without any restrictions.

Results

Patient Baseline Characteristics

Table 1 illustrates the baseline demographic characteristics of the two groups. From 1998 to 2016, a total of 1160 patients matched our inclusion criteria as outlined above. We used the X-tile software to calculate the following optimal cutoffs; for the age at diagnosis (Figure 7A), tumor size (Figure 7B), and years at diagnosis (Figure 7C). Of all patients, 819 (70.60%) patients were younger than nine years, whereas the remaining 341 (29.40%) were older than nine. Among these patients, 562 (48.45%) were male, and a total of 310 patients (26.72%) were diagnosed before the year 2003. Moreover, white was the predominant race. The tumor size in 166 (14.31%) patients was smaller than 25mm, whereas that of 449 (38.71%) patients was unknown. In 19 (1.64%) patients, the tumors were located in the left, and 18 (1.55%) in the right.

Multivariate cox regression results

At a ratio of 7:3, patients were randomly divided into training and validating groups, respectively. Next, we used the log-rank test to explain no significant survival difference between the training and validation groups ($p=0.9$). Subsequently, significant variables in the results of the stepwise-backward Cox regression model and multivariate-Cox regression analyses of CSS were entered into the construction of a nomogram. As illustrated in Figure 1 and Figure 2 (A-D), significant variables contained age at diagnosis, years at diagnosis, tumor size, and histological grade.

Nomogram construction and validation

As illustrated in Figure 2, the constructed nomogram showed that tumor size was the most vital factor influencing prognosis and was followed by the histological grade, age at diagnosis, and years at diagnosis, respectively. Subsequently, we applied the C-index to assess the performance of the nomogram. Here, the CSS prediction results showed that the C-index value in the training group was 0.649, whereas that of the validating group was 0.652. Among the training groups, 1-, 3-, and 5-year relative survival AUCs were 0.695, 0.803, and 0.803 (Figure 3A). On the other hand, as illustrated in Figure 3B, the validation group AUC values for the different years were 0.680, 0.835, and 0.843, respectively. As demonstrated in Figure 4, the calibration curves show excellent consistency between nomogram in CSS predictions and actual observations in 1-, 3-, and 5-year survival rates. Moreover, as shown in Figure 5, the DCA curves of 1-, 3-, and 5-year show that the CSS model could generate net benefits in the training and validation groups. Additionally, we conducted a risk group stratification of the total risk score calculated using the nomogram. Pediatric patients with BSMG were divided into two categories: low risk (total points ≤ 92.3) and high risk (total points > 92.3). A Kaplan-Meier product-limit estimate was applied to estimate the survival curve between two risk categories (Figure 6 E).

Discussion

Previously, studies have shown that malignant brainstem gliomas in pediatric patients have a poor prognosis.(Maxwell and Luksik et al., 2018; Khalid and Kelly et al., 2019) Therefore, there is a need to

discover a new complete prognostic scoring system for an accurate and useful prognosis assessment. A nomogram is a graphical representation of complex mathematical formulas.(Grimes, 2008) The nomogram showed much more convenience and accuracy when used in clinical applications. A higher C-index means a better predictive value.(Wang and Li et al., 2013; Zhu and Zhu et al., 2016) The nomogram utility has been assessed in many fields, like bladder cancer,(Yang and Bai et al., 2020) esthesioneuroblastomas,(Jiang and Lin et al., 2020) non-metastatic breast cancer,(Qian and Jia et al., 2020) or in neurosurgery of cancers like glioblastoma(Li and He et al., 2020) and so forth. Of note, this is the first research to introduce nomogram into pediatric primary BSMG before the onset of therapies.

It is commonly believed that the prognosis of cancer patients depreciates with age. Previous studies of adult patients with brainstem gliomas have shown that younger age is a prognostic factor for improved survival.(Guillamo and Monjour et al., 2001; Theeler and Ellezam et al., 2015; Esteve-Codina and Alameda et al., 2020) Doyle et al. reported that those patients whose age was more than 50 years significantly signified a worse prognosis than younger cohorts.(Doyle and Khalafallah et al., 2019) However, in pediatric patients, the situation was different. Our study showed that the patients older than nine years had a better prognosis. In our opinion, this could be due to the patient's younger age, which decreased their tolerance to the disease and treatment measures. Notably, the research by Sun et al. supported our findings. Here, a significantly better prognosis was observed in patients whose age was more than ten years.(Sun and Xu et al., 2020)

Regarding the size of the tumor, the large size (defined as tumors with dimensions greater than 25mm) was an independent predictor of mortality in our patient cohort. Maxwell et al. established that the tumor size, which was larger than 34mm was a significantly worse predictor of mortality in his cohort.(Maxwell and Luksik et al., 2018) Large size (>2 cm), enhancement, and invasion of adjacent brainstem structures on head MRI are signs of more aggressive tectal lesions(Rengachary and Rauf, 2012). Besides, the brainstem contained an extremely high density of critical structures.(Scott, 2004; Mukherjee and Antar et al., 2020) Nevertheless, as the tumor diameter increased, these critical structures are more likely to be compressed, which partly defined the surgiCal complexity.

Interestingly, pediatric BSMGs diagnosed after 2003 had a significantly better prognosis than that before 2003. It has been gradually recognized that brainstem gliomas comprise a heterogeneous group of tumors, and the patients could benefit from introducing the concept of precision and individualized therapeutic methods.(Wong and Brown et al., 2019) As the study progressed, a better understanding of the biology of BSMGs would improve treatment options and outcomes undoubtedly.(Reyes-Botero and Mokhtari et al., 2012) In previous studies, the biopsy is warranted in cases only when tumor progression. (Stark and Fritsch et al., 2005) Nevertheless, subsequent research suggested that brainstem stereotactic biopsy in children was a safe procedure and could alter the treatment recommendations.(Pincus and Richter et al., 2006) There is minimal long-term benefit from chemotherapy, and the mainstay of treatment for BSMGs is radiotherapy. After 2003, it has been demonstrated that the use of radiochemotherapy may improve treatment efficacy.(Marcus and Dutton et al., 2003; Sanghavi and

Needle et al., 2003; Bernier-Chastagner and Grill et al., 2005; Hargrave and Bartels et al., 2006) All of the abovementioned facts can directly lead to better survival among pediatrics diagnosed after 2003.

According to the 2016 World Health Organization (WHO) of the Central Nervous System Grading Standard, gliomas are divided into four grades (I–IV), depending on the histological and molecular features.(Louis and Perry et al., 2016) High-grade gliomas (WHO grade III-IV) are more aggressive and invasive than low-grade (WHO grade I-II), and high-grade brainstem gliomas have shown poorer survival rates in pediatrics(Jallo and Biser-Rohrbaugh et al., 2004; Sun and Wan et al., 2013), which is in line with our findings. Lesions with focal enhancement on head MRI in pediatric BSMGs were found mostly low-grade glioma.(Lesniak and Klem et al., 2003) Necrosis and inhomogeneous contrast enhancement were regarded as significant predictors of high-grade brainstem gliomas.(Moharamzad and Sanei Taheri et al., 2018) Recurrent mutations of a regulatory histone-H3F3A,(Schwartzentruber and Korshunov et al., 2012) gain of H3K27 methylation at p16INKA4A,(Chan and Fang et al., 2013) and upregulation of MYCN in G34R/v mutated(Bjerke and Mackay et al., 2013) were associated with carcinogenesis, tumor progression, and the risk of pediatric high-grade gliomas and had a significant effect on survival.

We divided pediatrics patients into low and high-risk groups according to their total points calculated from the nomogram. Kaplan Meier survival analysis showed significant differences in cancer-specific survival between low and high-risk groups. Thus, particular attention was given to these pediatric BSMGs with total points higher than 92.3 or tumor diameters larger than 2cm because of their poor outcomes.

In this study, we performed calibration and validation after the nomogram was constructed. Here, the receiver operating characteristics (ROC) were plotted using the calibration method, and the respective areas under the receiver operating characteristic curve (AUC) were calculated. The obtained calibration curve and high AUC values confirmed that our nomogram model was reliable, and its predicting capability was robust. Therefore, using these models, we can predict pediatric patients' survival with BSGM more accurately and provide the basis for individualized treatment for these patients. Finally, the DCAs of the nomogram in 1-, 3-, and 5-year show that net benefits could be obtained in both the training and validation cohorts.

This study has some drawbacks. First, our study was based on the SEER database. This database lacks some vital information on tumor biological data, such as MGMT (O (6)-methylguanine-DNA methyltransferase),(Jovanović and Mitrović et al., 2019) promoter methylation, and IDH (isocitrate dehydrogenase) mutations,(de Quintana-Schmidt and Alvarez-Holzzapfel et al., 2015) or H3 K27M,(Chi and Tarapore et al., 2019) which have substantial prognostic value in pediatric patients suffering from glioma. Secondly, it has no detailed description of the relationships with neurovascular structures and the precise location of the lesions in the brainstem. Thirdly, this is a retrospective study and cannot define causality. However, compared to other reported studies, it has the largest sample size, a strength.

Conclusion

Nomogram constructed with four variables in this study has a good performance. It is convenient, practical, and can help make the individual clinical decision and assess pediatric patients' risk with primary brainstem malignant glioma. This preoperatively predictive model was objective and accurate in predicting 1-, 3-, and 5-year CSS rates before treatment.

Declarations

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Conflicts of interest/Competing interests: The authors declare that no conflict of interest exists.

Availability of data and material: Clinicopathological data reported in this manuscript were collected from the SEER database. Copies of these data can be obtained free of charge from <https://seer.cancer.gov>.

Code availability: Not applicable.

Authors' contributions: Methodology, C.W.; software, C.W.; validation, L.C., L.J. and W.W.; formal analysis, C.W.; resources, C.W., L.C; writing—original draft preparation, C.W.; writing—review and editing, W.X., L.J.; supervision, W.X., L.J.; project administration, W.X. All authors have read and agreed to the published version of the manuscript.

Ethics approval: This study complies with the Declaration of Helsinki (World Medical Association Declaration of Helsinki). This study did not require ethics approval, as SEER database is publicly available and extraction of data from SEER were identified as nonhuman study.

Consent to participate: Not applicable as the SEER database was analyzed retrospectively.

Consent for publication: All the authors were agreed for publication freely.

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Tables

Characteristics	Categories	Total (%)	Training (%)	Validation (%)	P Value
Age	0y-9y	819(70.60)	568(69.95)	251(72.13)	0.456
	10y-18y	341(29.40)	244(30.05)	97(27.87)	
Years	Before 2003	310(26.72)	232(28.57)	78(22.41)	0.030
	After 2003	850(73.28)	580(71.43)	270(77.59)	
Sex	Male	562(48.45)	397(48.89)	165(47.41)	0.644
	Female	598(51.55)	415(51.11)	183(52.59)	
Race	White	864(74.48)	602(74.14)	262(75.29)	0.905
	Black	187(16.12)	132(16.26)	55(15.80)	
	Other	109(9.40)	78(9.61)	31(8.91)	
Histological grade	Low-grade	70(6.03)	44(5.42)	26(7.47)	0.236
	High-grade	84(7.24)	55(6.77)	29(8.33)	
	Mixed	1006(86.72)	713(87.81)	293(84.20)	
Size(mm)	≤25	166(14.31)	121(14.90)	45(12.93)	0.540
	>25	545(46.98)	374(46.06)	171(49.14)	
	Other	449(38.71)	317(39.04)	132(37.93)	
Laterality	Right	19(1.64)	13(1.60)	6(1.72)	0.699
	Left	18(1.55)	11(1.35)	7(2.01)	
	Other	1123(96.81)	788(97.04)	335(96.26)	
Months		12(7-27.25)	12(7-29.5)	12(7-26)	0.315

Table 1 Demographics and clinicopathological characteristics of Pediatric brainstem malignant gliomas.

Figures

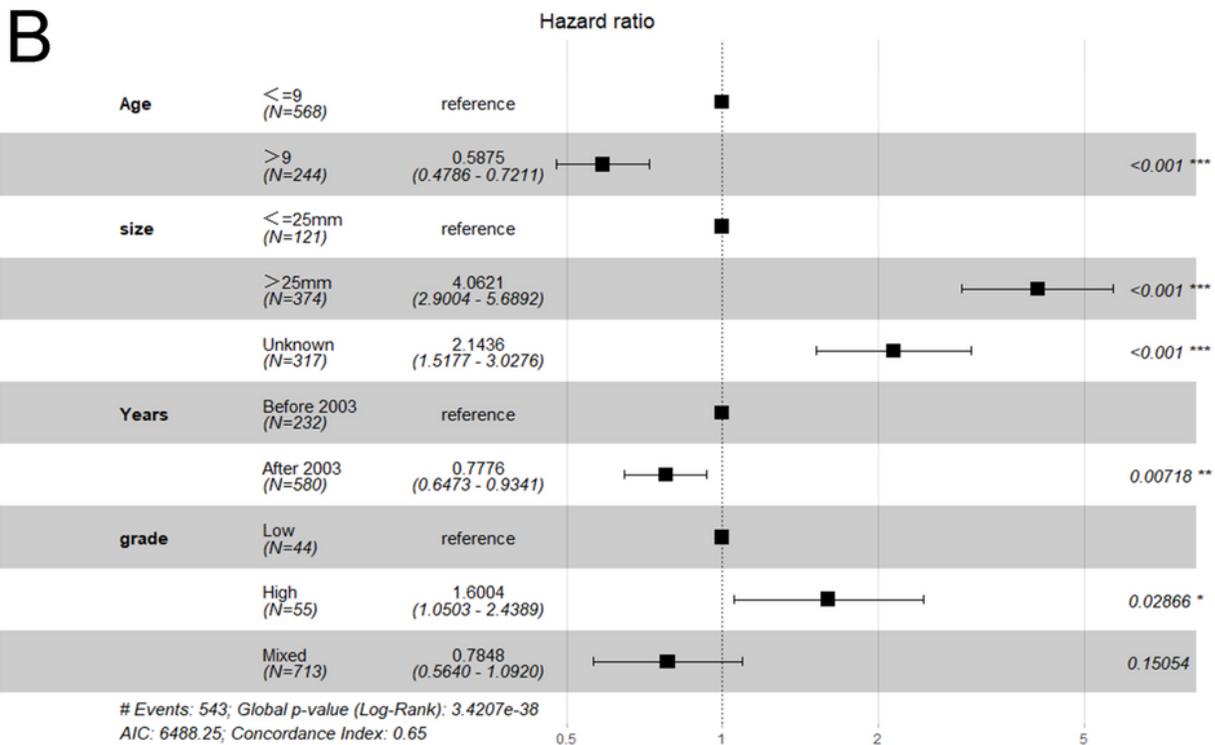
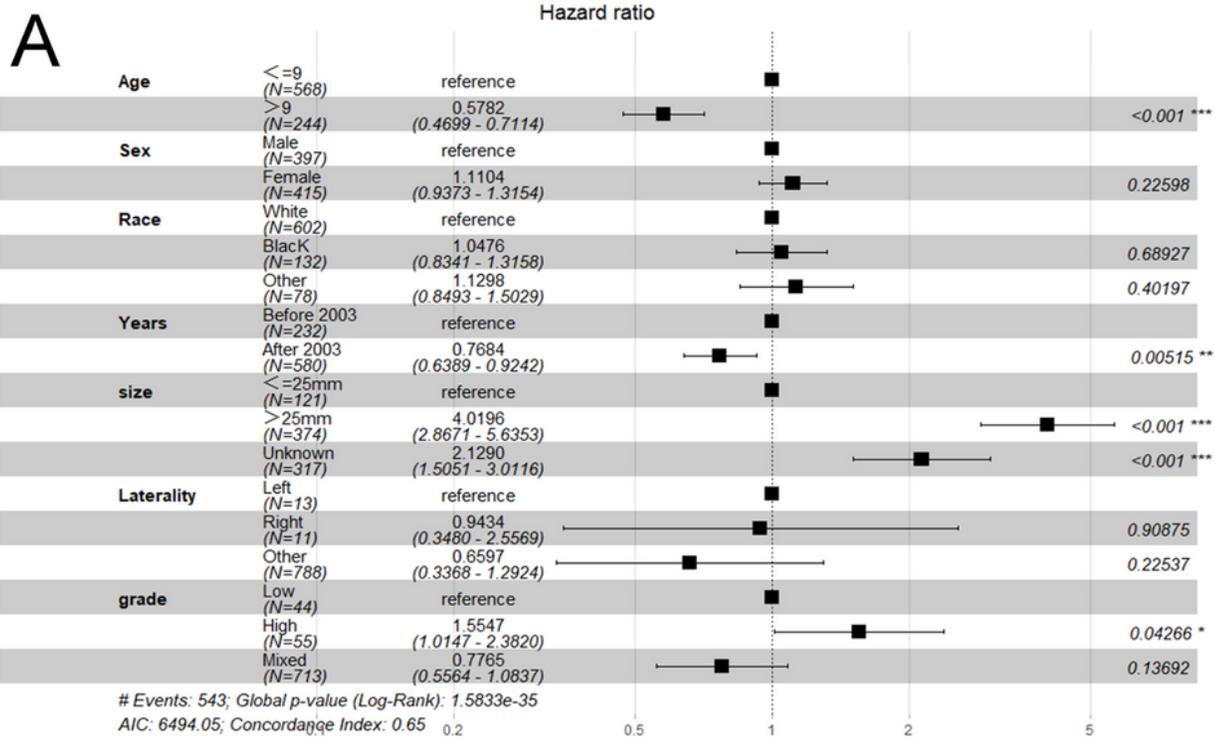


Figure 1

Multivariate Cox analysis (A) and backward stepwise regression analysis (B) of cancer-specific survival factors

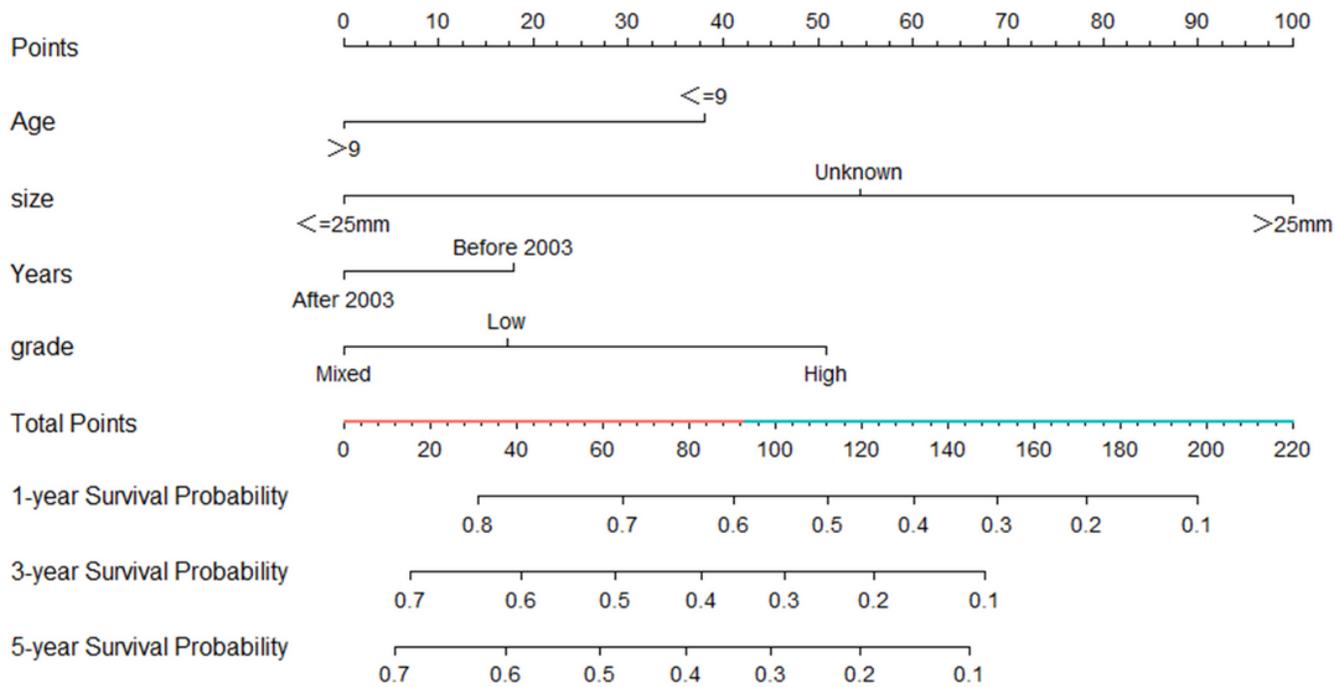


Figure 2

A developed nomogram for prognostic prediction of pediatric brainstem malignant gliomas cancer-specific survival rates at 1-, 3-, and 5-year. Patients were divided into two risk classifications: low risk (total points ≤ 92.3 , pink) and high risk (total point > 92.3 , blue).

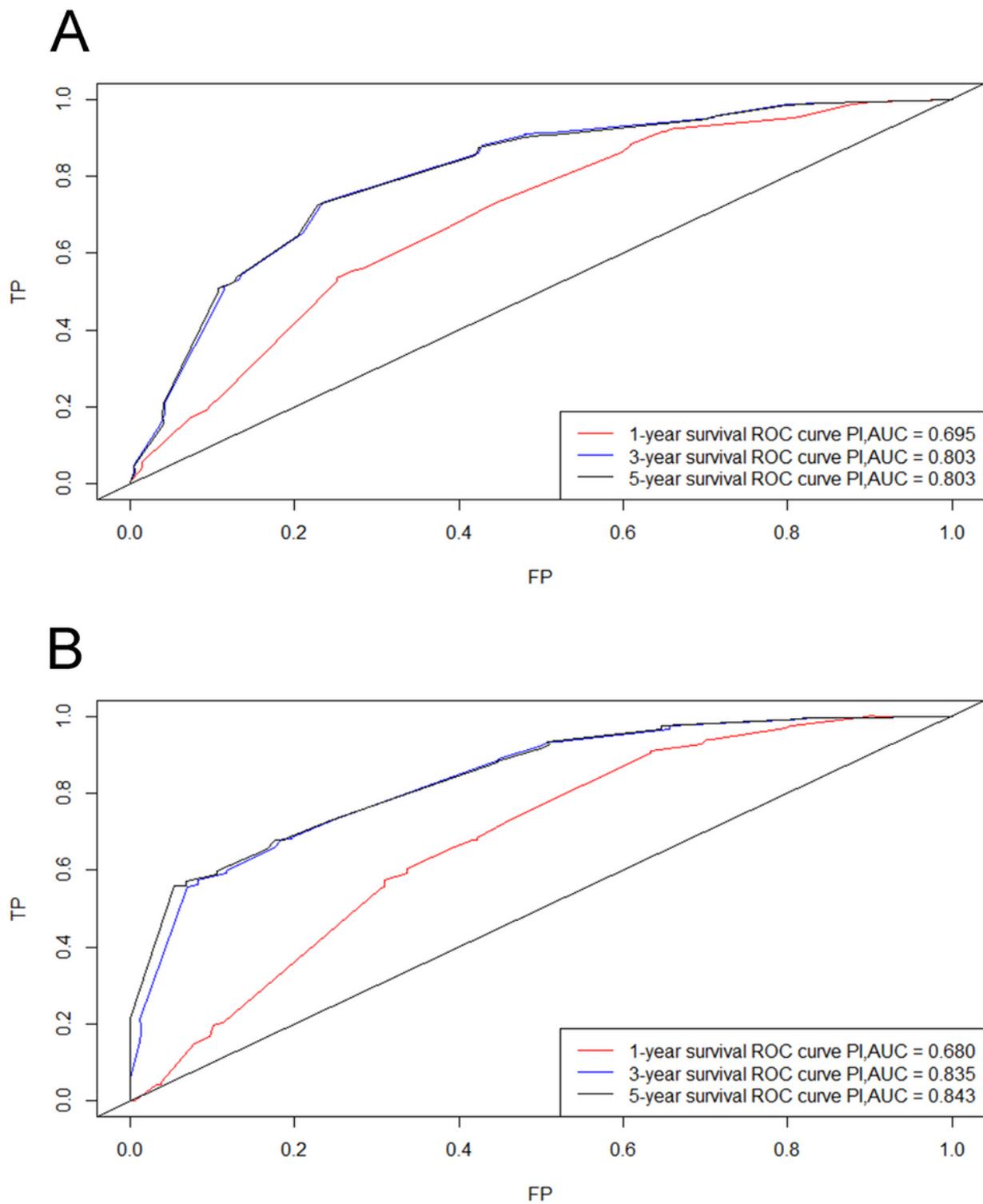


Figure 3

ROCs curve for nomograms. AUCs of the nomograms to predict cancer-specific survival at 1-, 3-, and 5-year using training dataset (A) and validation dataset (B).

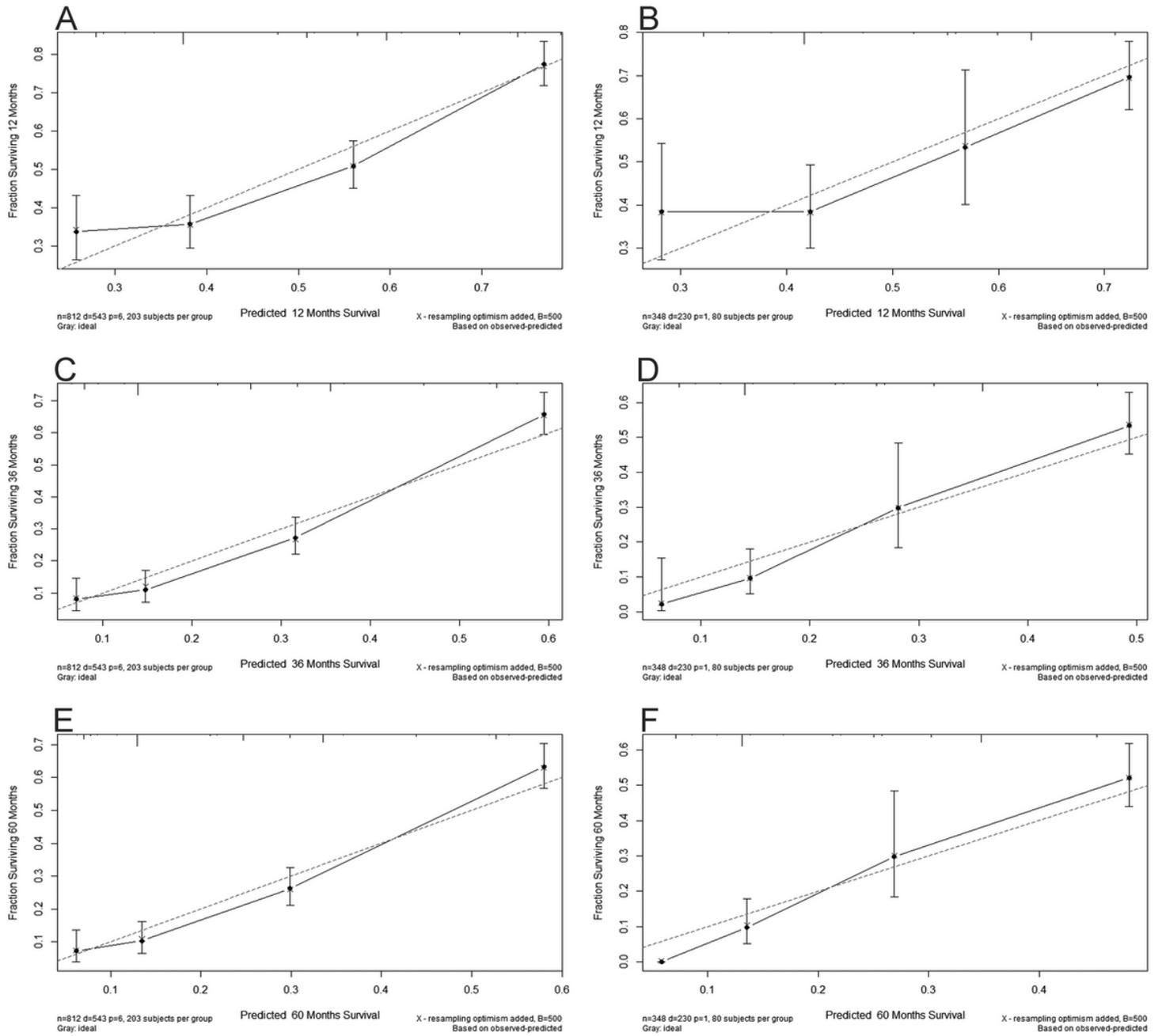


Figure 4

The calibration curves in training (A, C, E) and validation (B, D, F) cohorts show the nomogram with excellent predicting ability in 1-, 3-, and 5-year cancer-specific survival

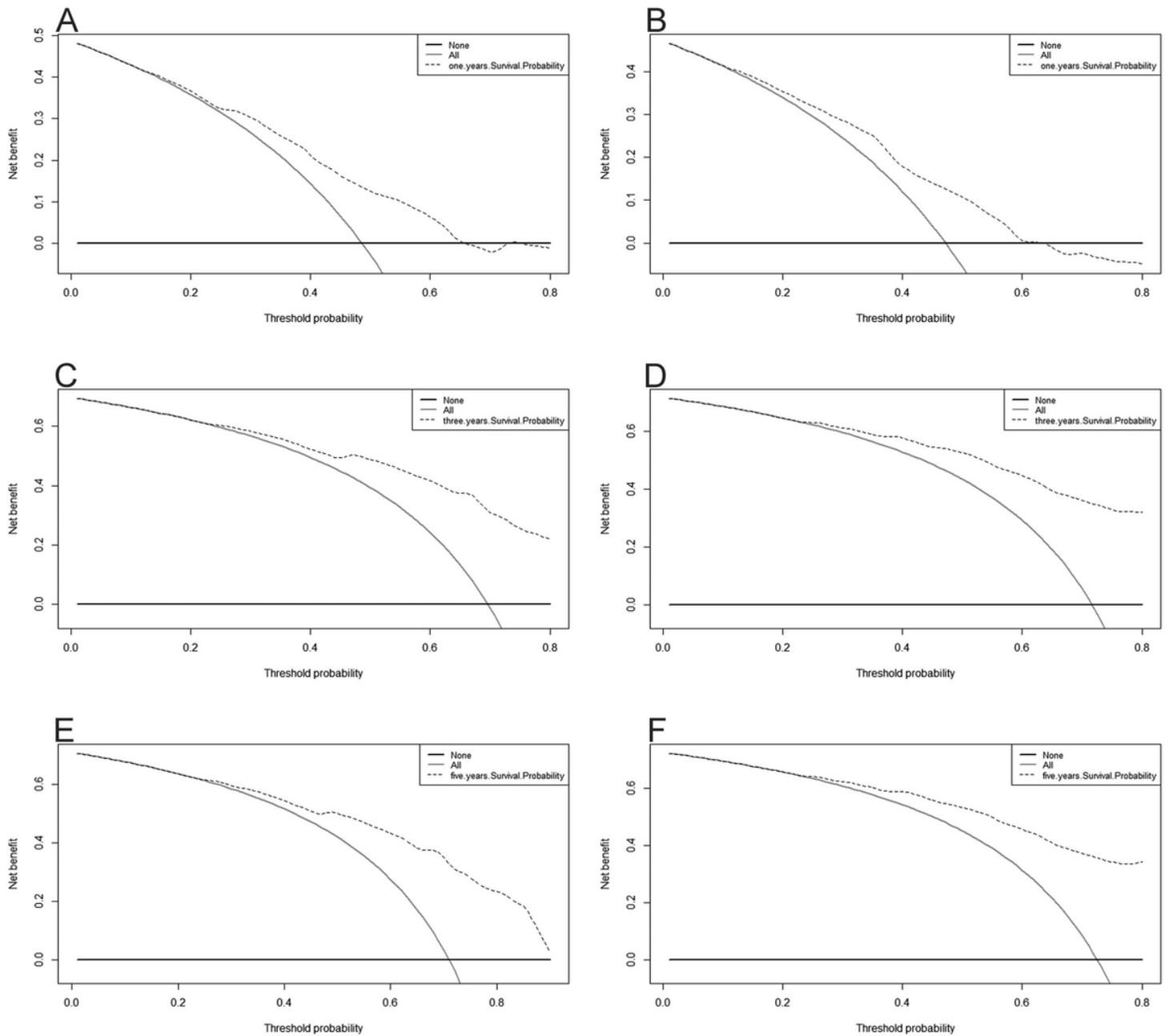


Figure 5

DCAs of a nomogram for cancer-specific survival in 1-, 3-, and 5-year show that both the training and validation cohorts could obtain net benefits. A, C, and E came from the training group, and the rest came from the validation group.

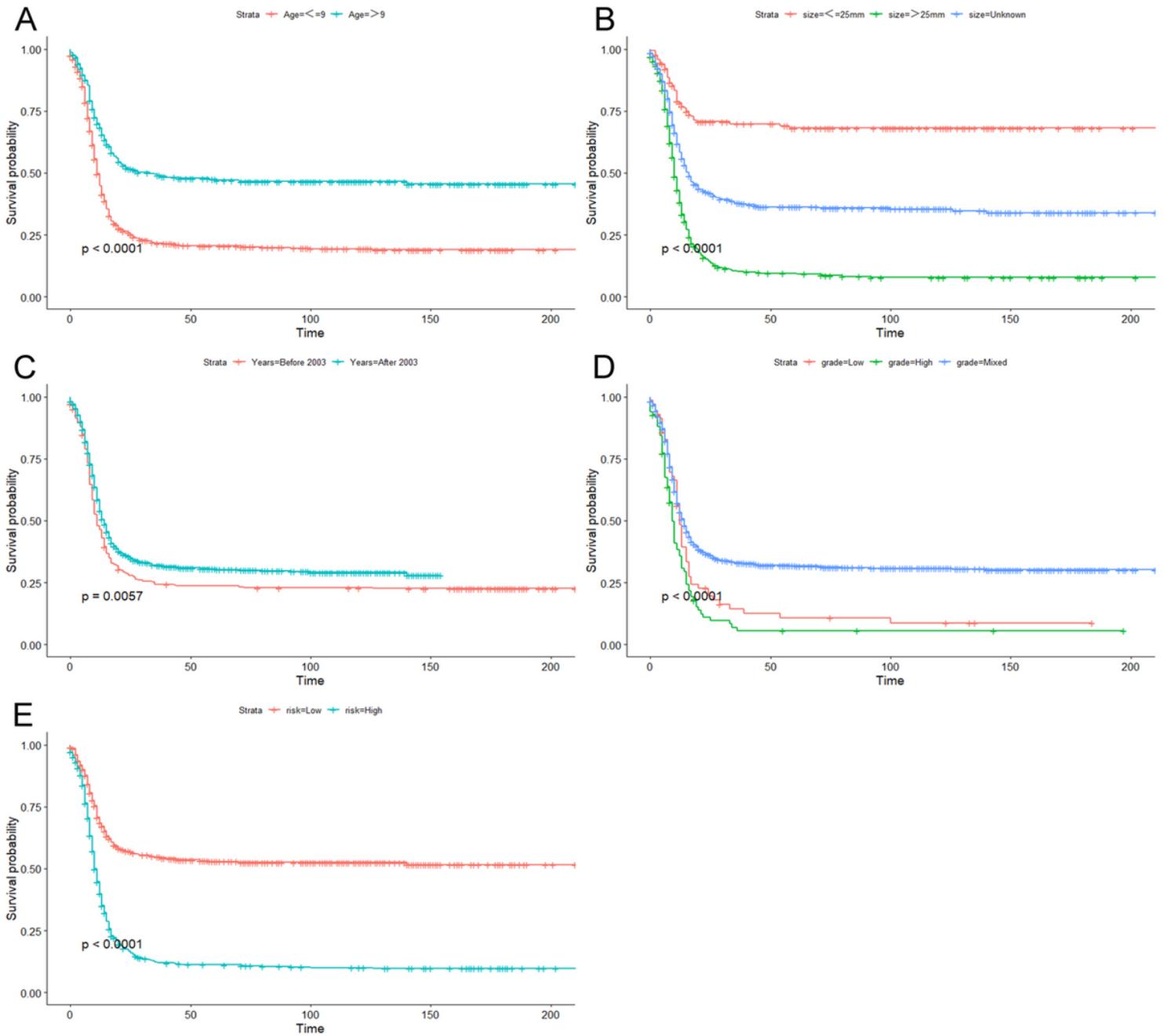


Figure 6

Kaplan–Meier cancer-specific survival curves of pediatric BSMGs stratified by age at diagnosis (A), tumor size (B), years at diagnosis(C), histological grade (D), and risk group stratification (E).

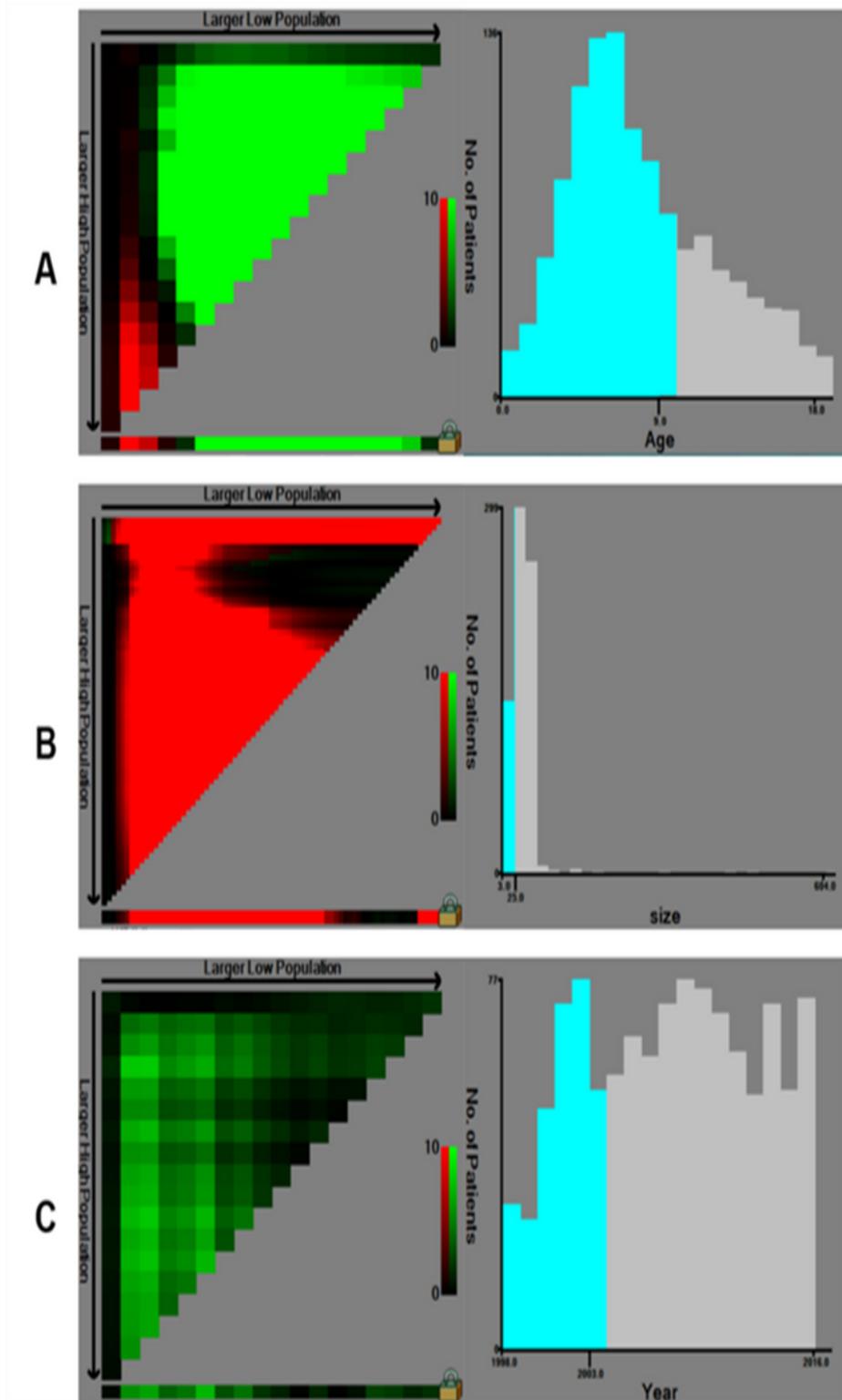


Figure 7

Age at diagnosis (A), tumor size (B) years at diagnosis (C) stratification using the X-tile software.