Clinical Article

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Clinical Nomogram Model for Predicting the Prognosis of Patients with Brainstem Glioma : A Population-based Study

Rui Zhang,[1,*] Gaoyue Jiang,[1,*] Yanming Ren,[1] Yuekang Zhang,[1] Xiaodong Niu[2]

Department of Neurosurgery,[1] West China Hospital, Sichuan University, Chengdu, China

Department of Neurosurgery and Department of Thoracic Surgery/Lung Cancer Center,[2] West China Hospital, Sichuan University, Chengdu, China

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Address for correspondence : **Xiaodong Niu**

Department of Neurosurgery and Department of Thoracic Surgery/Lung Cancer Center, West China Hospital, Sichuan University, Chengdu 610041, China

Tel : +86-, Fax : +86-, E-mail : niuxiaodong@wchscu.cn, ORCID : https://orcid.org/0000-0003-4750-812X

Yuekang Zhang

Department of Neurosurgery, West China Hospital, Sichuan University, Chengdu 610041, China

Tel : +86-, Fax : +86-, E-mail : 2012zykyx@sina.cn, ORCID : https://orcid.org/0000-0001-5709-3752

*These authors contributed equally: Rui Zhang, Gaoyue Jiang.

Abstract

Objective : The current understanding and clinical prediction of brainstem glioma (BSG) are still limited. This study aimed to conduct a large-scale population-based study to construct a clinical predictive model.

Methods : Patients with BSG diagnosed histologically from 1973 to 2016 were identified using the SEER database. According to WHO grade, the whole population was divided into the LGBSG cohort and the HGBSG cohort. Univariate and multivariate cox regression analyses were employed to determine prognostic factors of OS. All independently prognostic variables were further used to construct nomograms to predict the 1- and 2-year overall survival probability. The precision and reliability of the nomogram were evaluated by C-index and calibration plots.

Results : Cox regression analysis showed that four independent prognostic factors, were identified in the LGBSG cohort and two independent prognostic factors were identified in the HGBSG cohort. These independently prognostic factors and the main demographic data were further used to construct clinical nomograms for the LGBSG and HGBSG cohorts, respectively. The C-index for the internal validation was 0.89 (95%CI, 0.83-0.95) and 0.64 (95%CI, 0.60-0.68) in the LGBSG and HGBSG cohorts, respectively. The results of the calibration plots showed that the actual observation and prediction values obtained by the nomogram had good consistency in the LGBSG and HGBSG cohorts.

Conclusion : This study identified several independent prognostic variables and further constructed the clinical nomogram model. The nomogram model can provide valuable clinical reference and risk assessments for clinicians to further manage these patients with BSG.

Key Words : Brainstem glioma · SEER · Nomogram · Overall survival · Prognosis.

INTRODUCTION

Brainstem glioma (BSG) is a heterogeneous group of central nervous system (CNS) tumor[20,23,28]. BSGs account for 4.3% of all gliomas as recorded in the recent report and are more commonly encountered in children[8,37]. Owing to the specific anatomical location of BSGs, these lesions impose substantial clinical consequences, with a notably high incidence of cranial nerve deficits[11]. And meanwhile, patients with these tumors typically demonstrate poor prognosis, particularly those with high-grade BSG (HGBSG).

Based on the World Health Organization Classification of Tumors of the Central Nervous System 5th Edition (WHO CNS5)[31], the integration of molecular profiling with histopathological evaluation has emerged as a transformative paradigm in contemporary glioma diagnostics[34,44]. For instance, Histone H3 Lysine 27 to Methionine-altered diffuse midline glioma (H3K27M-DMG) is a typical tumor, which is one of the common types in BSG and associated with dismal prognosis due to be high infiltration and less amenable to surgery[6,16,18,33]. Pediatric and adult BSGs demonstrate distinct clinicopathological characteristics[15,17]. For example, pediatric H3K27M-DMG patients have a poorer survival prognosis compared to adult patients[15]. However, accumulative evidence reported that pathological classification exerts a more substantial impact on survival outcomes than age-related factors. The patients with HGBSG in pediatric or adult have a worse survival outcome compared to the low-grade BSG

(LGBSG)[26,39].

Over the last decades, increasing studies characterized the clinicopathologic features, treatment modalities and prognostic factors of BSGs[39,42]. However, there is no consensus on the benefits of treatment modalities and no exclusive clinical prediction model for BSGs mainly due to its being unusual and limited sample size. Considering these situations, a publicly available database of SEER (Surveillance Epidemiology and End Results) may address this challenge. Thus, a search was performed on the SEER database and a total of 730 patients with BSG were identified and included in this study for survival analysis and constructing the clinical prediction model of overall survival (OS). To date, it is the first BSG-specific nomogram stratified by WHO grade, which could contribute to optimizing the clinical management of these patients.

MATERIALS AND METHODS

Study population

Clinical data of patients were retrieved from the 18 registries within the SEER database (1973–2016) using SEER*Stat 8.3.6 software, which is one of the largest publicly available cancer data sets. The International Classification of Diseases for Oncology, third edition (ICD-O-3), was used to screen brainstem glioma cases using the site codes and histological codes. From the SEER database, we included cases with histologically confirmed brainstem glioma, including pilocytic astrocytoma (PA), oligodendroglioma, astrocytoma, anaplastic oligodendroglioma (AO), anaplastic astrocytoma (AA), and glioblastoma (GBM, including

gliosarcoma). Patients without main survival data, including age, sex, survival time, and status, were excluded. Cases with glioma described as only being involving the partial brainstem structure were also excluded from the study, and these tumors may not originate from brainstem. This study did not require review by our institutional review board because the SEER database is publicly and freely available.

Variables of interest

The included cases were described based on the following variables of interest: patient demographic data (age, sex, race, marital status, insurance), tumor characteristics (histopathology, grade, number of tumors, tumor size, and tumor extent), treatment data (surgical resection, radiation, and chemotherapy). Several variables were classified according to the codes in the SEER database and described previously. Along with being analyzed as a continuous variable, age was categorized into three groups: <18 years, 18-65 years, and ≥65 years. The median value of tumor size was used as the cutoff value. The race was divided into white, black, or other according to the SEER categories. Tumor extent (or stage) of disease by SEER categories was defined as local and distant involvement. Local tumors strictly confined to the brainstem parenchyma, while distant indicates lesions extending beyond the brainstem with invasion of surrounding anatomical structures. Tumor grade was divided into low-grade glioma (LGG, including grade I and II), high-grade glioma (HGG, including grade III and IV). Regarding the treatment course, the extent of resection was recorded as gross total resection (GTR), subtotal resection (STR), partial resection (PR), or no resection according to previously described schemes.

Construction of nomograms

Due to the significant difference between different tumor grade, the whole population was divided into two cohorts, LGBSG and HGBSG, for the survival analysis and construction of nomograms. For two cohorts, univariable and multivariable analyses were used to identify independent prognostic factors of OS. Along with these variables, including age, sex, and treatments, were included to construct the nomogram of two groups, respectively. The authenticity and reliability of the nomogram model were evaluated by calculating the Harrell's concordance index (C-index). The value of C-index ranges from 0.5 to 1.0, with higher C-index indicating a more perfect discrimination ability. Calibration plots were constructed to assess the consistency between the predicted and observed values.

Statistical analysis

All statistical analyses were performed using SPSS software (version 24, SPSS Inc., Chicago, IL, USA) and R software (version 3.3.4, http://www.R-project.org). For continuous measures, the variables were summarized as the mean±SD or median (25^{th}, 75^{th}). The Chi-squared test and Student's t-test were used to compare categorical variables and continuous variables. Kaplan-Meier curves were constructed and analyzed using the log-rank test. Univariate and multivariate Cox proportional hazards regression analyses were performed on clinical variables to determine the independent prognostic factors. The nomograms were constructed using the "survival" and "rms" package in R. All statistical tests were two-sided, and P value < 0.05 was considered as statistical significance.

RESULTS

Clinical characteristics of patients

A total of 730 patients with a diagnosis of BSG from 1973 to 2016 from the SEER database were identified and included in the present study. The flow diagram used for data selection is shown in Fig. 1. Of these 730 patients, 408 were divided into low-grade BSG (LGBSG) cohort and 322 divided into high-grade BSG (HGBSG) cohort according to the WHO grade. Of these enrolled patients, 394 were male (54.0%) and 336 were female (46.0%). In addition, 391 (53.6%) were aged <18 years, 298 (40.8%) were aged 18-65 years, and 41 (5.6%) were aged ≥65 years. According to WHO grade, 359 patients (49.2%) had grade I, 49 (6.7%) had grade II, 143 (19.6%) had grade III, and 179 (24.5%) had grade IV. For the surgery, 153 (21.0%) patients had GTR, 315 patients (43.1%) had PR/STR, 47 patients (6.4%) had surgery, NOS, and the remaining (215, 29.5%) had no surgery. Of these patients, 215 (29.5%) patients had undergone radiotherapy and 248 (34.0%) patients had undergone chemotherapy. The clinical data from all patients and two cohorts stratified by WHO grade was summarized in Table 1.

Survival analysis and cox regression analysis

The median OS of all patients is 27.0 months. The median OS of the LGBSG cohort is 99.5 months, whereas the median OS of the HGBSG cohort is 9.0 months. Kaplan-Meier analysis was used to determine the impact of variables on OS in the LGBSG cohort and HGBSG cohort, respectively (Fig. 2 and 3). Notably, pediatric patients with LGBSG demonstrate

significantly better clinical outcomes compared to their adult counterparts. In contrast, both pediatric and adult populations with HGBSG exhibit uniformly poor prognoses.

In the LGBSG cohort, univariate cox regression analysis revealed a significant difference in OS between subgroups of several variables, including age, grade, tumor extent, surgery, and radiotherapy. A multivariate cox regression analysis further showed age, tumor extent, surgery, and radiotherapy were the independent prognostic factors. Same as the LGBSG cohort, univariate and multivariate cox regression analysis showed that age and surgery were independent prognostic factors of OS (Table 2 and Fig. 4).

Nomograms construction and evaluation

Combined with independent prognostic factors of OS in two cohorts, the nomogram model for predicting the OS rate was constructed, respectively. In the LGBSG cohort, a nomogram for predicting the 1- and 2-year OS rates was developed using the 6 variables (Fig. 5). The nomogram revealed that age was the most strongly associated with the prognosis, followed by the surgery, radiotherapy, tumor extent, sex, and grade. It is worth noting that patients receiving radiotherapy had poorer survival compared to no radiotherapy. The C-index for the internal validation was 0.89 (95%CI, 0.83-0.95), and calibration plots of 1- and 2-year survival probability showed that the actual observation and prediction values of the present nomogram exhibited good consistency in the LGBSG cohort (Fig. 5). Also, a nomogram for predicting the 1- and 2-year survival probability was developed using the 5 variables in the HGBSG cohort (Fig. 6). The nomogram of the HGBSG cohort revealed that age was also the most strongly associated with the prognosis. In this cohort, the patients receiving radiotherapy had better

survival, which is not consistent with the LGBSG cohort. The C-index for the internal validation was 0.64 (95%CI, 0.60-0.68). And the actual observation and prediction values of the present nomogram also exhibited good consistency in the HGG cohort (Fig. 6).

DISCUSSION

Brainstem gliomas are more commonly encountered in children than in adults[16,37]. BSGs have a poor prognosis, especially for HGG patients due to higher invasive ability and heterogeneity[26,35,39]. Patients with various clinical clinicopathologic features and treatment modalities would have different survival outcomes. To date, several studies have depicted the clinical and prognostic features in pediatric or adult BSGs[21,26,35,39]. However, little is known about the clinical prediction model of survival in BSG patients. A nomogram is an applied graphic score tool that can be used as a clinical prediction model, which can allow clinicians to easily calculate the total score and predict the survival probability of individual patients[3,13,14].

No matter in pediatric or adult BSG patients, the marked differences were observed in the clinical characteristics and prognosis between LGG and HGG patients[9,39]. In the present study, a total of 730 BSGs were classified into the LGBSG cohort and HGBSG cohort to conduct the survival analysis and construct the clinical nomogram, respectively. A Cox regression analysis was first used to determine the independent prognostic factors. In the LGBSG cohort, four independent prognostic factors, including age, tumor extent, surgery, and radiotherapy, are identified. Meanwhile, two independently prognostic factors including grade and surgery, are identified in the HGBSG cohort. These independently prognostic factors were further used to

construct the nomograms.

In the present study, age (<18/≥18 years) was the most significant independent prognostic factor in the LGBSG cohort and older patients had poorer survival outcomes. Although age was not an independent prognostic factor in the HGBSG cohort, there was a trend similar to the LGBSG patients. For example, in LGBSG patients, one retrospective study including 48 pediatric patients showed a median OS of 177.6 months[1]. Another study including adult LGBSG patients reported that the median OS of 26.2 months for grade II and the median OS of 83 months for grade I[25,29,39]. Our conclusion that pediatric patients have better survival than adult patients, was consistent with the results of other clinical studies. Besides, a previous study revealed that age distribution was associated with the isocitrate dehydrogenase (IDH) mutation in LGG patients[41]. However, as the data of molecular markers were not available in the SEER database, the association between age and IDH mutant was not analyzed in the present study.

WHO grade of gliomas is also an important prognostic factor and high grade represents the worse outcome. In the HGBSG cohort, WHO grade was the main independent prognostic factor, and grade IV had the worse outcome compared to the grade III patients. However, multivariate analysis showed no significant statistical difference in OS between grade I and II in the LGBSG cohort. These results were consistent with the related studies published previously[26,29,39]. Besides, tumor extent (local or distant) is also an important prognostic factor in gliomas. In the present study, Cox regression analysis shows that the tumor extent was an independent prognostic factor in the LGBSG cohort and a distant extent indicated a worse outcome. Similarly, glioma patients with distant extent located in the other sites also had poor survival outcome, indicating the progression or late stage of the disease[7].

Treatments of BSGs mainly include surgery, radiotherapy, chemotherapy, and others. However, to date, there remain some controversies concerning the treatment regimens of these tumors. Similar to the thalamic tumors, surgical treatment of the brainstem tumor has often been considered difficult due to its critical position and crucial neurologic function[8,22,36]. However, advances in neuroimaging techniques and surgical assistance techniques have made resection of brainstem tumors feasible. Previous studies revealed that GTR played an important role in the management of glioma patients including BSG, and was considered to be a favorable predictor of better OS[36,43]. Based on our present analysis, cox regression analysis showed that surgery was an independent prognostic factor in the LGBSG and HGBSG cohorts, respectively. In the HGBSG cohort, GTR was significantly associated with the best OS, however, GTR was not significantly associated with the best OS in the LGBSG cohort. Due to GTR indicating the high risk of neurologic impairment[17], which is also an important prognostic factor, GTR may not provide superior clinical outcomes compared to STR in patients with LGBSG. Same as supratentorial gliomas, especially located in or close to the functional areas, the maximal resection of the tumor was performed, meanwhile the protection of neurologic function should be concerned[10]. From this study, we speculated that the protection of neurologic function should be more concerned with the surgery of LGBSG patients that HGBSG patients.

Besides, previous studies showed that radiotherapy may prolong the survival of BSG patients[12]. Based on our analysis, radiotherapy can benefit HGBSG patients. Other studies also confirmed the same results[46]. However, radiotherapy was an independent prognostic factor in the LGBSG cohort. Radiotherapy for gliomas with a good prognosis may increase the risk of neurocognitive side effects in the long term[27]. Besides, the endocrine dysfunction caused by

radiotherapy cannot be ignored[27]. Meanwhile, some previous studies reported the use of different regimens of radiotherapy in BSG patients, and they may have different outcomes[12,19]. Due to these data not available from the SEER database, the comparison of different regimens of radiotherapy can't be performed. For patients with LGBSG, a comprehensive risk-benefit assessment of radiotherapy remains to be thoroughly investigated. Furthermore, the optimal radiation dosage parameters require precise determination. Chemotherapy also is used as an alternative option to treat BSGs. The present study revealed chemotherapy was not an independent prognostic factor in the LGBSG and HGBSG cohorts. Only a few cases were reported to have a good response to chemotherapy[32]. To overcome these hardships and challenges, increasing basic studies and clinical trials are being in progress to challenge the BSGs[4,24].

Nomograms are useful, accessible, and objective tools, that can be used to predict survival, plan treatment, and decide the follow-up interval. To date, nomograms have been previously developed for gliomas, including GBM and LGG[13,14]. Same as nomograms developed previously, the nomogram developed in the present study can provide a simple and intuitive predictive model for individual patients with BSG, and allowed clinicians to easily calculate the total prognostic score quantitatively. Additionally, the effectiveness and reliability of the nomogram model were authenticated by discrimination and calibration. The nomogram of the LGBSG cohort in the present study exhibited good predictive ability due to high C-index and consistency between the predicted and observed values. In the HGBSG cohort, the nomogram showed a relatively low prediction effect compared to the LGBSG cohort. Previous studies reported that the nomogram for individually predicting the prognosis of high-grade gliomas

(HGG) exhibits superior predictive accuracy[5,45]. This may be associated with the brainstem-specific challenges, such as inoperability and IDH-wildtype prevalence. Generally, these two nomograms provided a predictive model for the clinicians to easily evaluate the survival probability of BSGs.

H3K27M-DMG is an added classification that combines gene mutations and histopathological features in the WHO classification of CNS tumors in 2016[30]. Due to the database that we used in this study, we didn't have much discussion. According to our team's previous report, we found that factors affecting the survival prognosis of H3K27M-DMG patients include age, preoperative KPS score, radiotherapy, and Ki-67 expression level, and constructed a nomogram[38]. Previous studies have indicated that there is significant difference between this particular tumor type and other BSGs[2,40]. Therefore, when examining this tumor, it is imperative to conduct a separate analysis.

Limitations

Nevertheless, there were some limitations to the present study. This nomogram model required external validation using other independent patients. Given the rarity of BSGs, it remains particularly challenging to acquire a sufficient clinical cohort from other datasets available. Therefore, our current model also can provide preliminary reference values for affected patients at present. Moving forward, we plan to validate these findings through prospective collection of real-world clinical data. In addition, the present model included partial patients of all BSGs due to excluding the patients with incomplete data, which may result in a selective bias. The SEER database demonstrates significant racial imbalance in BSG cases, with

White individuals constituting 84.4% of the study population, potentially introducing selection bias. Moreover, some important parameters, such as the Karnofsky performance score (KPS) and molecular markers (IDH1/2, and 1p/19q, et al.) were not available from the SEER database, so that the prognostic role of these factors can't be evaluated. Besides, this study only included pathologically confirmed BSGs. However, given that a subset of BSGs were inoperable and even biopsy-inaccessible, we were unable to characterize this patient population. Finally, the analysis of potential interaction or confounding effects among key variables remains limited. For instance, given that age was a significant prognostic factor in the LGBSG cohort, additional analyses, such as stratified assessments or modeling with interaction terms, could elucidate whether the distribution of surgical methods or radiotherapy varies across age groups. Such analyses would help determine whether these variations might bias (overestimate or underestimate) the independent prognostic influence of age.

CONCLUSION

We have identified several independent prognostic factors of OS and further constructed a nomogram model for predicting OS for individual patients with LGBSG and HGBSG, respectively. The nomogram model can provide valuable clinical reference and risk assessments for clinicians to further manage these patients with BSG.

AUTHORS' DECLARATION

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Informed consent

This type of study does not require informed consent.

Data sharing

None

Preprint

None

ORCID

Rui Zhang https://orcid.org/0009-0003-4154-4522

Gaoyue Jiang https://orcid.org/0009-0003-5488-4454

Yanming Ren https://orcid.org/0000-0001-8099-0339

Yuekang Zhang https://orcid.org/0000-0001-5709-3752

Xiaodong Niuhttps://orcid.org/0000-0003-4750-812X

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Figure legends

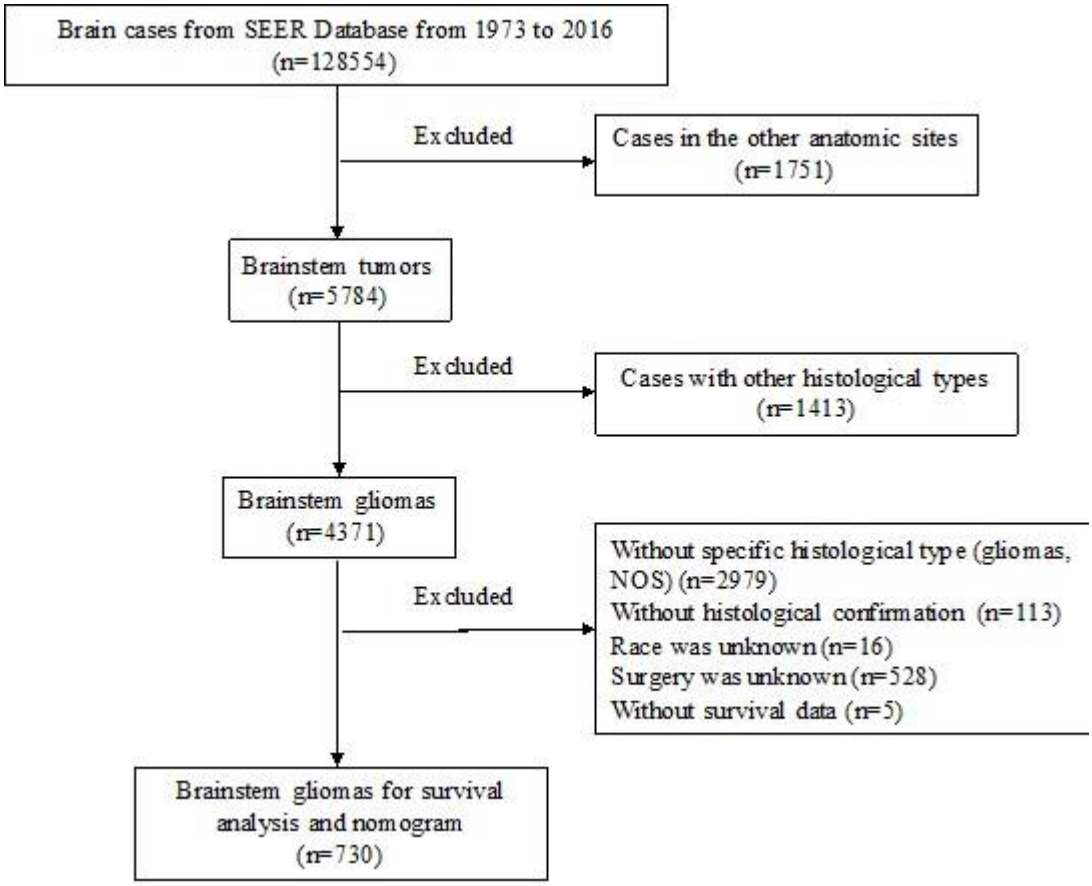

Fig. 1. The flow diagram of cases inclusion and exclusion from the SEER database.

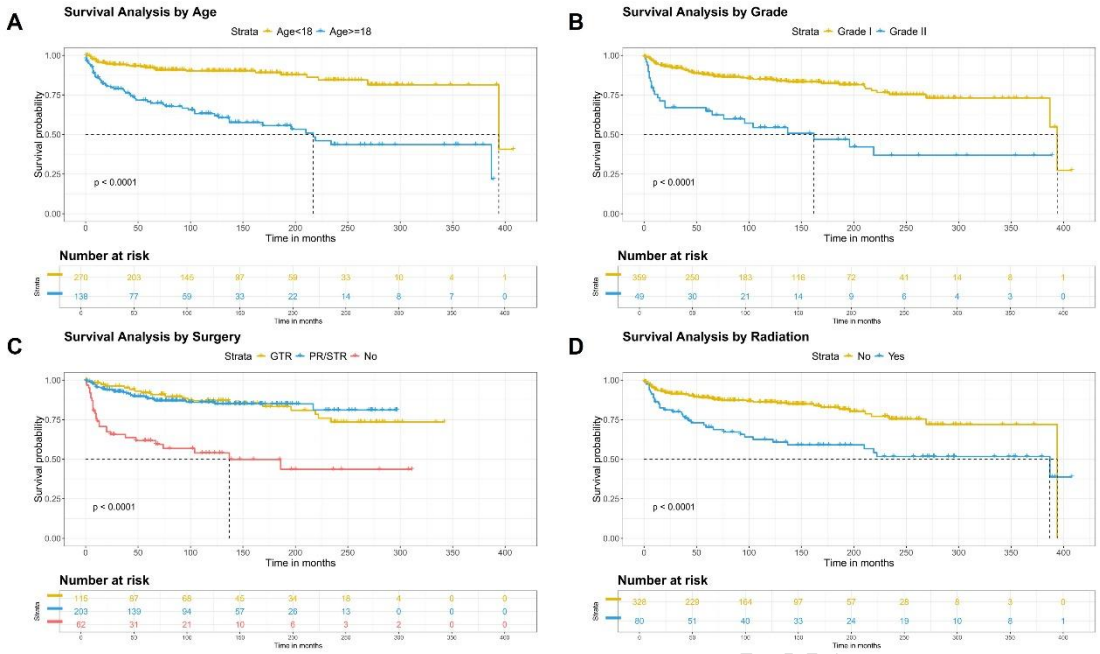

Fig. 2. Kaplan-Meier analysis determining the impact of variables on OS in LGBSG cohort. A: Kaplan–Meier survival curve stratified by age (P<0.001). B: Kaplan–Meier survival curve stratified by grade (P<0.001). C: Kaplan–Meier survival curve stratified by surgery (P<0.001). D: Kaplan–Meier survival curve stratified by radiotherapy (P<0.001).

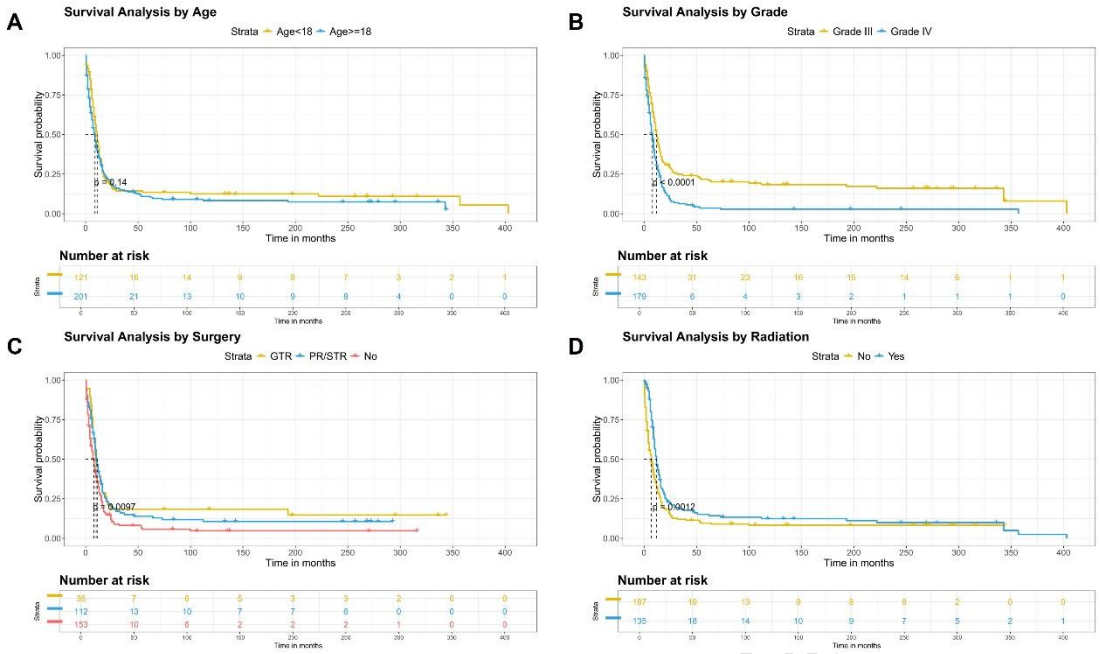

Fig. 3. Kaplan-Meier analysis determining the impact of variables on OS in HGBSG cohort. A: Kaplan–Meier survival curve stratified by age (P=0.145). B: Kaplan–Meier survival curve stratified by grade (P<0.001). C: Kaplan–Meier survival curve stratified by surgery (P=0.010). D: Kaplan–Meier survival curve stratified by radiotherapy (P=0.001).

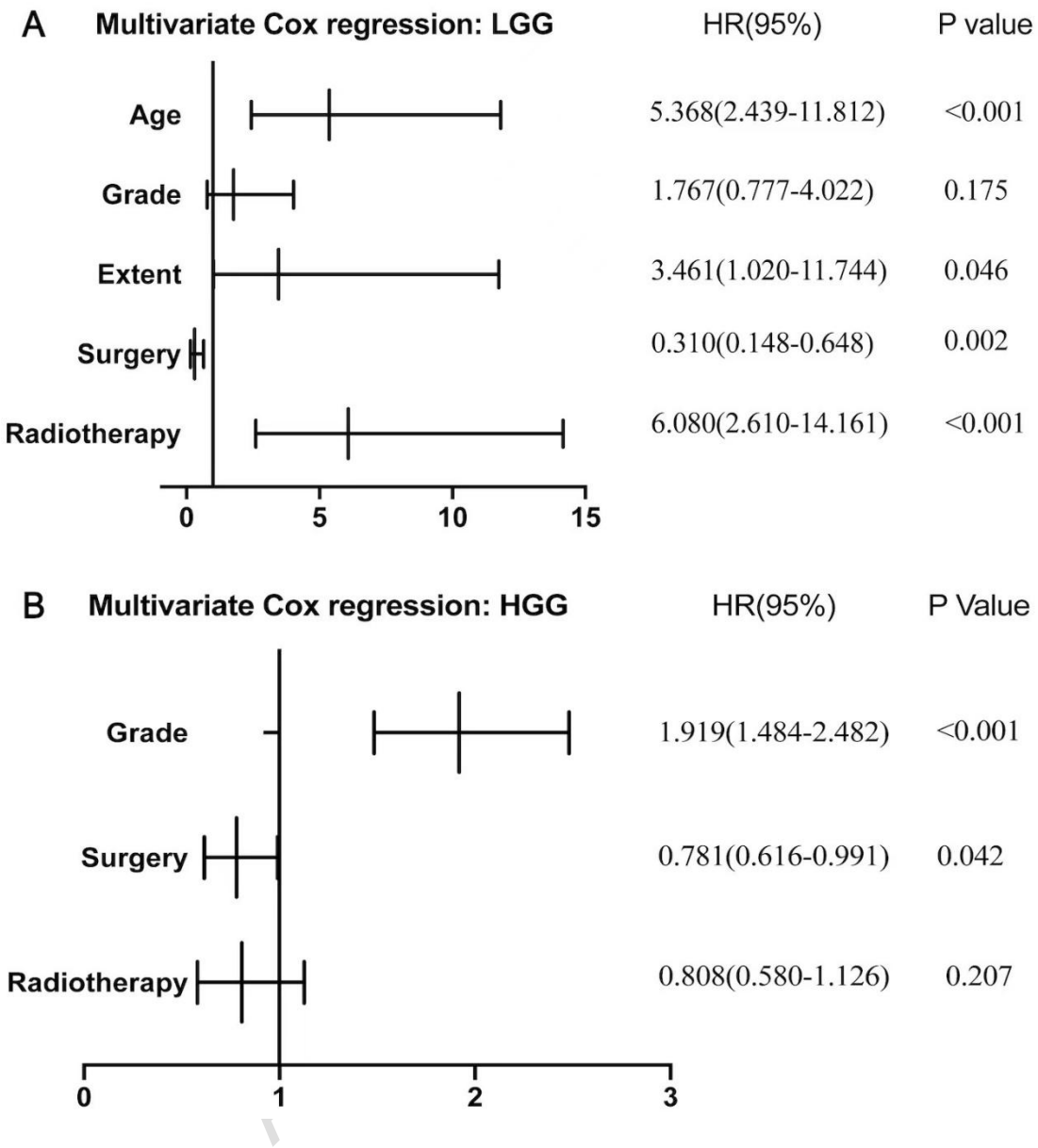

Fig. 4. Multivariate cox regression analysis of variables on OS. A: Multivariate cox regression analysis in LGBSG cohort. B: Multivariate cox regression analysis in HGBSG cohort.

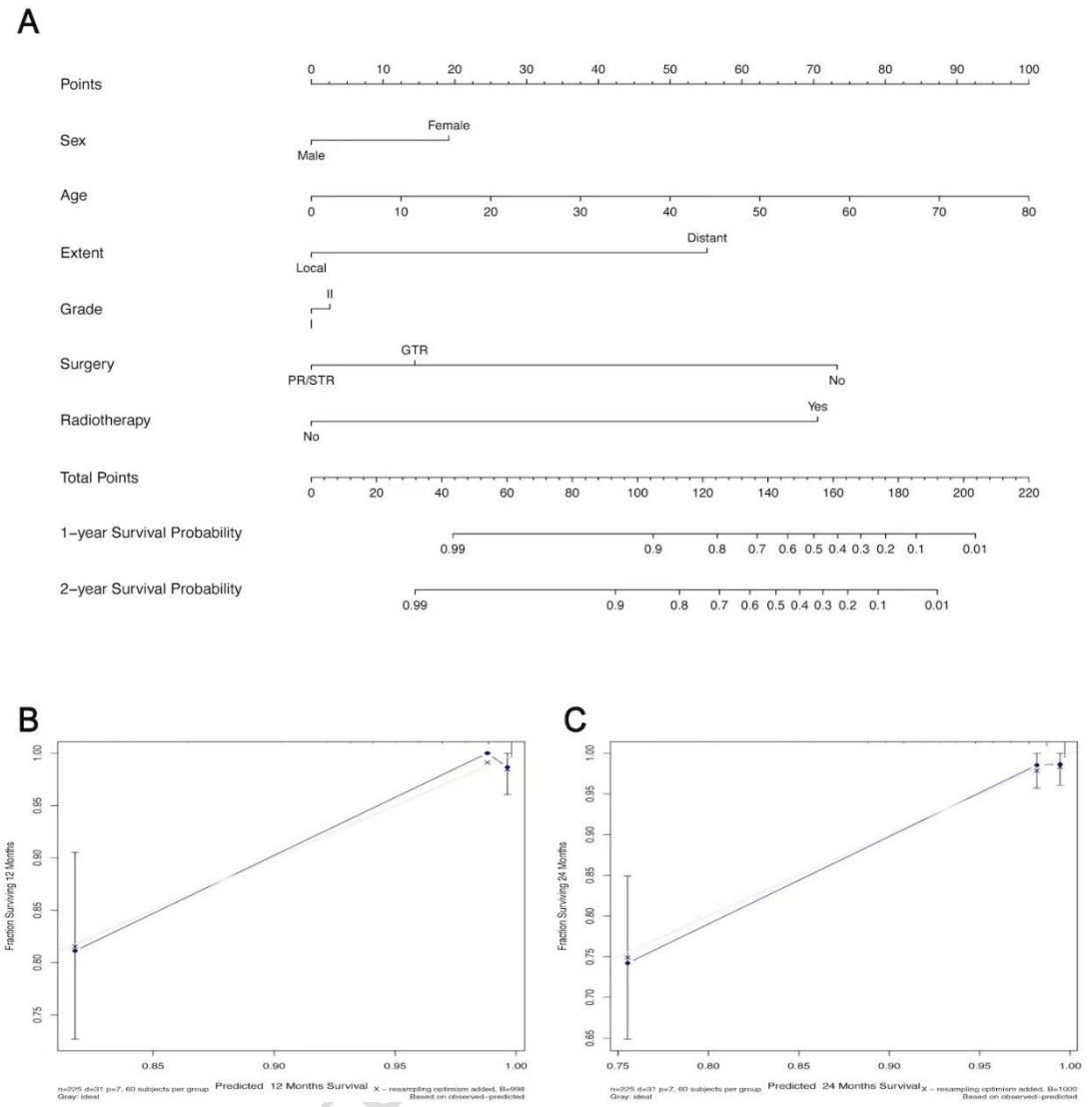

Fig. 5. A Nomogram model and calibration plots of 1- and 2-year survival probability in the LGBSG cohort. A: Nomogram model in the LGBSG cohort. The C-index for the internal validation was 0.89 (95%CI, 0.83-0.95). B and C: Calibration plots of 1- and 2-year survival probability showing good consistency in the LGBSG cohort.

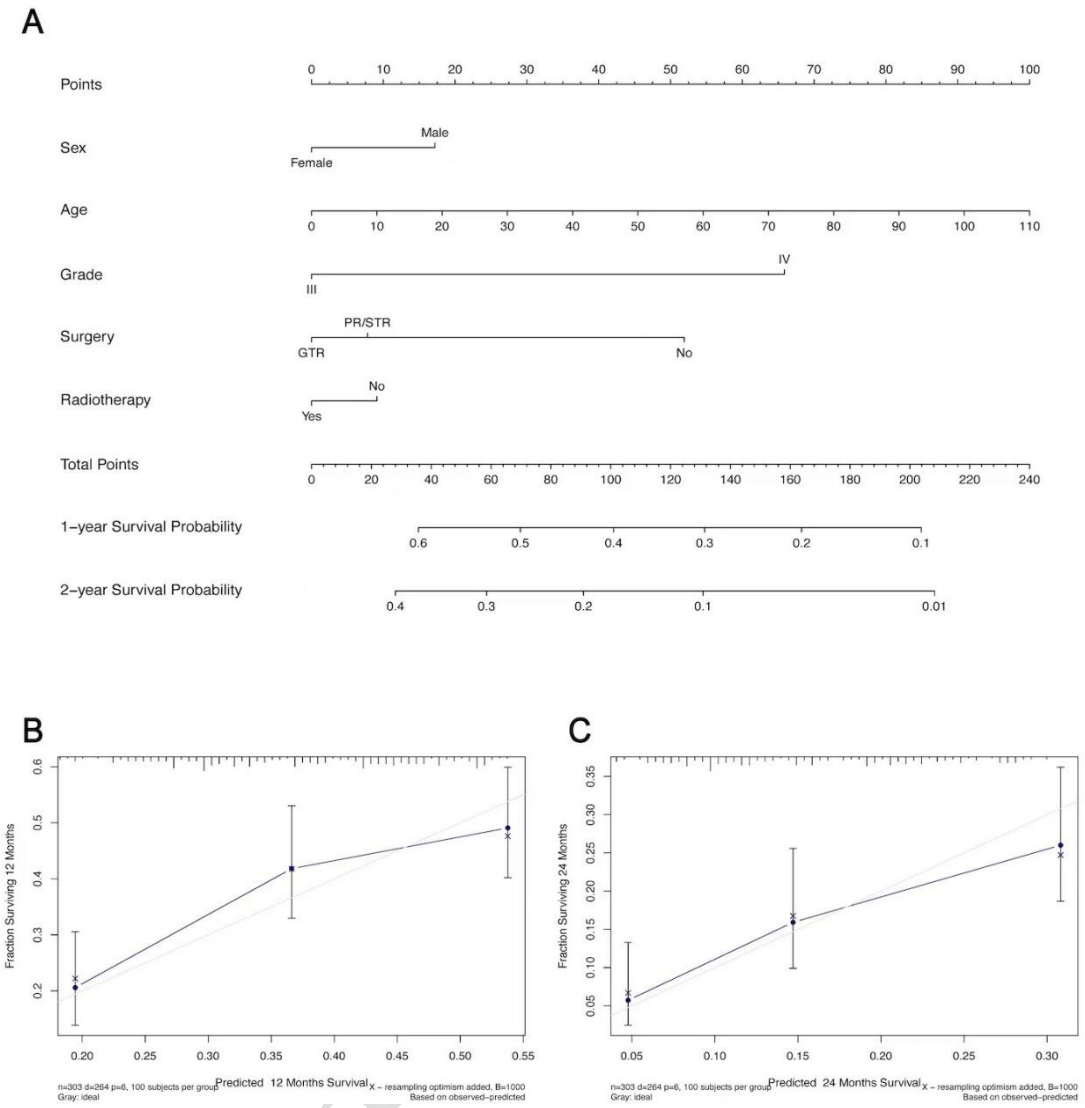

Fig. 6. A nomogram model and calibration plots of 1- and 2-year survival probability in the HGBSG cohort. A: Nomogram model in the HGBSG cohort. The C-index for the internal validation was 0.64 (95%CI, 0.60-0.68). B and C: Calibration plots of 1- and 2-year survival probability showing that the actual observation and prediction values of the present nomogram in the HGBSG cohort.

Tables

Table 1. Summary of clinicopathologic features and treatments of BSG patients

Variable	All	LGBSG	HGBSG
Total	730 (100%)	408 (55.9%)	322 (44.1%)
Age at diagnosis			
Median (25th, 75th) (years)	16 (6, 41)	12 (5, 22)	34 (8, 54)
<18 years	391 (53.6%)	270 (37.0%)	121 (16.6%)
18-65 years	298 (40.8%)	131 (17.9%)	167 (22.9%)
≥65 years	41 (5.6%)	7 (1.0%)	34 (4.6%)
Sex			
Male	394 (54.0%)	210 (28.8%)	184 (25.2%)
Female	336 (46.0%)	198 (27.1%)	138 (18.9%)
Race			
White	616 (84.4%)	358 (49.0%)	258 (35.4%)
Black	71 (9.7%)	33 (4.5%)	38 (5.2%)
Other	43 (5.9%)	17 (2.3%)	26 (3.6%)
Marital status			
Single or Divorced	532 (72.9%)	344 (47.1%)	188 (25.8%)
Married	187 (25.6%)	57 (7.8%)	130 (17.8%)
Unknown	11 (1.5%)	7 (1.0%)	4 (0.5%)
Insurance			

Insured	220 (30.1%)	117 (16.0%)	103 (14.1%)
Uninsured	97 (13.3%)	54 (7.4%)	43 (5.9%)
Unknown	413 (56.6%)	237 (32.5%)	176 (24.1%)
WHO grade			
I	359 (49.2%)	359 (49.2%)	-
II	49 (6.7%)	49 (6.7%)	-
III	143 (19.6%)	-	143 (19.6%)
IV	179 (24.5%)	-	179 (24.5%)
Tumor size			
Median (25^{th}, 75^{th}) (mm)	32 (23.5, 42)	34 (24.75, 45)	30 (22, 40)
Tumor extent			
Local	395 (54.1%)	218 (29.9%)	177 (24.2%)
Distant	11 (1.5%)	8 (1.1%)	3 (0.2%)
Unknown	324 (44.3%)	182 (24.9%)	142 (19.4%)
Surgery			
GTR	153 (21.0%)	115 (15.8%)	38 (5.2%)
PR/STR	315 (43.1%)	203 (27.8%)	112 (15.3%)
No	215 (29.5%)	62 (8.5%)	153 (21.0%)
Surgery, NOS	47 (6.4%)	28 (3.8%)	19 (2.6%)
Radiotherapy			
Yes	215 (29.5%)	80 (11.0%)	135 (18.5%)
No/unknown	515 (70.5%)	328 (44.9%)	187 (25.6%)

Chemotherapy			
Yes	248 (34.0%)	80 (11.0%)	168 (23.0%)
No/unknown	482 (66.0%)	328 (44.9%)	154 (21.1%)

NOS: not otherwise specified

Table 2. Univariate cox regression analyses of OS in the LGBSG and HGBSG cohorts

Variables	LGBSG cohort		HGBSG cohort	
	χ^2	P value	χ^2	P value
Age at diagnosis				
<18/≥18 (years)	41.928	**<0.001**	1.987	0.159
Sex				
Male/ Female	0.010	0.918	1.847	0.174
Race				
White/Black/Other	0.237	0.627	0.031	0.859
Insurance				
Insured/Uninsured/ Un	0.038	0.864	1.412	0.235
WHO grade				
I/ II	28.293	**<0.001**	-	
III/ IV	-	-	22.328	**<0.001**
Tumor size*				
<34/≥34 (cm)	1.432	0.231	-	-
<30≥/30 (cm)	-	-	0.194	0.659
Tumor extent				
Local/ Distant/ Un	4.246	**0.039**	0.286	0.593
Surgery				
GTR/(PR/STR)/No	20.368	**<0.001**	7.643	**0.006**
Radiotherapy				

Yes/No	16.097	**<0.001**	9.700	**0.002**
Chemotherapy				
Yes/No	1.793	0.181	0.541	0.462

*The median of size is as cutoff value. Un: Unknown.