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Clinical nomogram for predicting the survival of patients with cerebral anaplastic gliomas

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Abstract

The present study aimed to develop an effective nomogram for predicting the overall survival (OS) of patients with cerebral anaplastic glioma (AG).

This study included 1939 patients diagnosed with AG between 1973 and 2013 who were identified using the Surveillance, Epidemiology, and End Results database. A multivariate Cox regression analysis revealed that age, histology, tumor site, marital status, radiotherapy, and surgery were independent prognostic factors and, thus, these factors were selected to build a clinical nomogram. Harrell's concordance index (C-index) and a calibration curve were formulated to evaluate the discrimination and calibration of the nomogram using bootstrapping.

A nomogram was developed to predict 5- and 9-year OS rates based on 6 independent prognostic factors identified in the training set: age, tumor site, marital status, histology, radiotherapy, and surgery ($P < .05$). The Harrell's concordance index values of the training and validation sets were 0.776 (0.759–0.793) and 0.766 (0.739–0.792), respectively. The calibration curve exhibited good consistency with the actual observation curve in both sets.

Although the prognostic value of the World Health Organization (WHO) classification has been validated, we developed a novel nomogram based on readily available clinical variables in terms of demographic data, therapeutic modalities, and tumor characteristics to predict the survival of AG patients. When used in combination with the WHO classification system, this clinical nomogram can aid clinicians in making individualized predictions of AG patient survival and improving treatment strategies.

Abbreviations: AA = anaplastic astrocytoma, AG = anaplastic glioma, AO = anaplastic oligodendroglioma, C-index = Harrell's concordance index, IDH = isocitrate dehydrogenase, KPS = Karnofsky performance status, NOS = not otherwise specified, OS = overall survival, SEER = surveillance, epidemiology, and end results, WHO = World Health Organization.

Keywords: anaplastic gliomas, nomogram, prognosis, SEER

1. Introduction

Anaplastic gliomas (AGs) account for approximately 6 to 15% of all primary brain tumors[1–6] and include 3 subtypes: anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and anaplastic oligoastrocytoma.[7–9] The median age at AG diagnosis is approximately 40 years old and surgery, radiotherapy, and chemotherapy are the current first-line treatments.[10] Favorable factors associated with the prognosis for AG include oligodendroglia histology, a young age, complete surgical resection, the 1p/19q codeletion, high Karnofsky performance status (KPS) score, and the isocitrate dehydrogenase (IDH)-1/2 mutation.[7,8,11] However, other important factors, including gender, race, tumor location, tumor size, and marital status, may also influence this prognosis.[12] Fortunately, these clinical variables are readily available and easily understood by both patients and clinicians. Because AG is diagnosed in young adults and this population has a long overall survival (OS) rate, clinicians must consider a wide variety of independent prognostic factors and the effects of these factors on OS. Therefore, the establishment of a clinical prognosis model based on readily available clinical variables will be of great significance for accurate predictions regarding the prognoses of AG patients.

The nomogram model is well suited to fulfill these requirements. Recently, clinical nomograms have been constructed to quantify risk based on various important and independent

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The original data used to support the findings of this study are available from the corresponding author upon request.

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prognostic factors in the field of oncology. Some studies have shown that clinical nomograms are more effective and accurate than traditional grading systems.[13–16] However, to date, clinical nomograms are rarely used for predicting the survival of AG patients.

Because AA and AO are the primary AG subtypes and most cases of AG are located in the cerebral hemispheres.[10,17–19] the subjects included in the present study were mainly diagnosed with AA or AO in the cerebral hemisphere. In the present study, the Surveillance, Epidemiology, and End Results (SEER) database was used to construct a clinical nomogram for AG. However, this database does not yet provide information on molecular markers, KPS scores, or chemotherapy and, therefore, these three variables were not evaluated as independent prognostic factors.

2. Methods

2.1. Study population

Clinical data were obtained using the SEER database (1973–2013) and the contents and criteria of the included variables were coded as follows:

(1) age at diagnosis (codes: 00–85+);
(2) histological types: AA (code: 9401) and AO (code: 9451);
(3) primary-site labeled: frontal lobe (code: C71.1), temporal lobe (code: C71.2), parietal lobe (code: C71.3), and occipital lobe (code: C71.4);
(4) RX Summ–Surg Prim Site: gross total resection (codes: 030 and 055), partial resection (codes: 020, 021, and 040), and no surgery (code: 000);
(5) tumor size (codes: 004–097, 100, 104, and 991–995);
(6) race: White, Black, American Indian/Alaska native, and Asian/Pacific Islander;
(7) sex: male and female;
(8) radiation sequence with surgery: Yes (codes: radiation after surgery, radiation before and after surgery, radiation prior to surgery, and sequence unknown but both were given) and No (codes: no radiation and/or cancer-directed surgery);
(9) survival months: (codes: 0–199);
(10) vital status (dead or alive); and
(11) marital status: married, divorced, separated, single, unmarried or domestic partner, and widowed.

After the final selection, a total of 1939 patients were enrolled as the original AG cohort.

2.2. Statistical analysis

All 1939 patients were randomly divided into training (70%) and validation (30%) sets using a random seed set at 2019. Univariate analyses of the clinical variables between the training and validation sets were conducted using Chi-square tests. Univariate and multivariate Cox proportional hazards regression analyses were performed on clinical variables in the training set. Harrell's concordance index (C-index), which is similar to the area under the receiver operating characteristic curve (AUC), was used to evaluate discrimination, and a higher C-index value (range: 0.5–1) was indicative of better discrimination. Additionally, calibration plots were constructed to assess consistency between the predicted and observed survival rates and the 5- and 9- year predicted survival probabilities based on the nomogram. All statistical analyses were conducted using SPSS software, version 25 (IBM Corporation; Chicago, IL) and *R* software (version 3.3.0, Institute for Statistics and Mathematics; Vienna, Austria). *P* values $< .05$ were considered to indicate statistical significance.

3. Results

3.1. Patient baseline characteristics

Based on the screening criteria, 1939 patients were identified using the SEER database and initially enrolled in the present study. For each individual year from 2004–2013, 193, 176, 200, 148, 184, 189, 190, 205, 226, and 228 cases were selected, respectively. The 1939 patients were randomly divided into 2 sets: the training set (70%; n = 1357) and the validation set (30%; n = 582). In the training set, the median follow-up was 44 months

Table 1

Patient demographics and clinical characteristics.

Variables	All patients n = 1939 (%)	Training set n = 1357 (%)	Validation set n = 582 (%)	*P* value
Age				.176
≤49	965 (49.8)	689 (50.8)	276 (47.4)	
≥50	974 (50.2)	668 (49.2)	306 (52.6)	
Sex				.926
Male	1063 (54.8)	743 (54.8)	320 (55)	
Female	876 (45.2)	614 (45.2)	262 (45)	
Race				.737
White	1722 (88.8)	1203 (88.7)	519 (89.2)	
Non-white	217 (11.2)	154 (11.3)	63 (10.8)	
marital status				.886
Married	1178 (60.8)	823 (60.6)	355 (61)	
Unmarried	761 (39.2)	534 (39.4)	227 (39)	
tumor site				.969
Frontal lobe	1088 (56.1)	760 (56.0)	328 (56.4)	
Temporal lobe	469 (24.2)	331 (24.4)	138 (23.7)	
Parietal lobe	317 (16.3)	222 (16.4)	95 (16.3)	
Occipital lobe	65 (3.4)	44 (3.2)	21 (3.6)	
Histology				.689
AA	1355 (69.9)	952 (70.2)	403 (69.2)	
AO	584 (30.1)	405 (29.8)	179 (30.8)	
Tumor size				.009
≤3cm	570 (29.4)	380 (28)	190 (32.6)	
>3≤5cm	692 (35.7)	513 (37.8)	179 (30.8)	
>5cm	677 (34.9)	464 (34.2)	213 (36.6)	
Radiotherapy				.443
Yes	1201 (61.9)	833 (61.4)	368 (63.2)	
No	738 (38.1)	524 (38.6)	214 (36.8)	
Surgery				.563
Gross total resection	658 (33.9)	466 (34.3)	192 (33)	
Partial resection	874 (45.1)	601 (44.3)	273 (46.9)	
No surgery	407 (21)	290 (21.4)	117 (20.1)	
Year of diagnosis				.68
2004	193 (10.0)	141 (10.4)	52 (8.9)	
2005	176 (9.1)	131 (9.7)	45 (7.7)	
2006	200 (10.3)	134 (9.9)	66 (11.3)	
2007	148 (7.6)	98 (7.2)	50 (8.6)	
2008	184 (9.5)	133 (9.8)	51 (8.8)	
2009	189 (9.7)	126 (9.3)	63 (10.8)	
2010	190 (9.8)	135 (9.8)	55 (9.5)	
2011	205 (10.5)	145 (10.7)	60 (10.4)	
2012	226 (11.7)	153 (11.3)	73 (12.5)	
2013	228 (11.8)	161 (11.9)	67 (11.5)	

Note: Non-white includes black, American Indian/Alaska native, Asian/Pacific Islander; unmarried includes divorced, separated, single, unmarried or domestic partner, widowed: AA = anaplastic astrocytoma, AO = anaplastic oligodendroglioma.

Table 2

Univariate and multivariate analyses of clinical variables in the training set.

Variables	Univariate analysis HR (95% CI)	*P*-value	Multivariate analysis HR (95% CI)	*P*-value
Age		<.001		<.001
≤49	Reference		Reference	
≥50	4.245 (3.578–5.035)		3.638 (3.027–4.372)	
Sex		.54		.878
Male	Reference		Reference	
Female	1.050 (0.899–1.225)		0.992 (0.847–1.163)	
Race		.975		.973
White	Reference		Reference	
Non-White	1.004 (0.786–1.283)		1.006 (0.784–1.290)	
Marital status		.811		.004
Married	Reference		Reference	
Unmarried	0.981 (0.837–1.150)		1.267 (1.074–1.496)	
Tumor site		<.001		<.001
Frontal lobe			Reference	
Temporal lobe	1.799 (1.499–2.160)		1.390 (1.153–1.674)	
Parietal lobe	1.914 (1.558–2.351)		1.365 (1.106–1.683)	
Occipital lobe	2.556 (1.732–3.770)		1.923 (1.297–2.850)	
Histology		<.001		<.001
AA	Reference		Reference	
AO	0.497 (0.412–0.600)		0.503 (0.411–0.615)	
Tumor size		<.001		.758
≤3cm	Reference		Reference	
>3≤5cm	0.760 (0.632–0.914)		1.007 (0.835–1.214)	
>5cm	0.605 (0.497–0.737)		1.036 (0.842–1.274)	
Radiotherapy		<.001		<.001
Yes	Reference		Reference	
No	2.428 (2.079–2.834)		1.676 (1.330–2.111)	
Surgery		<.001		<.001
Gross total resection	Reference		Reference	
Partial resection	1.760 (1.437–2.156)		1.501 (1.221–1.845)	
No surgery	5.060 (4.090–6.261)		1.990 (1.485–2.665)	

CI = confidence interval, HR = hazard ratio.

(range: 0–119 months) and the 5- and 9-year survival rates were 44.0% and 36.0%, respectively. In the validation set, the median follow-up was 39 months (range: 0–119 months) and the 5- and 9-year survival rates were 43.3% and 31.0%, respectively. The demographics and tumor characteristics for all patients, patients in the training set, and patients in the validation set are summarized in Table 1.

3.2. Independent prognostic factors in the training set

A univariate Cox regression analysis of the clinical variables revealed that age, tumor site, tumor size, histology, radiotherapy, and surgery were significant factors ($P < .05$; Table 2). Additionally, a multivariate Cox regression analysis revealed that the hazard ratios were significantly higher for age, tumor site, marital status, histology, radiotherapy, and surgery ($P < .05$; Table 2, Fig. 1). Therefore, 6 independent prognostic factors (age, tumor site, marital status, histology, radiotherapy, and surgery) were screened out.

3.3. Nomogram construction

The present study developed a nomogram for predicting 5- and 9-year OS rates in AG patients based on 6 independent prognostic factors from the training set that had significant hazard ratios (Fig. 2). The nomogram revealed that age had the greatest effect on AG prognosis followed by histology, surgery, tumor site, radiotherapy, and marital status. Each independent prognostic factor corresponded to a score on the points scale and the cumulative score of the independent prognostic factor scores were able to predict 5- and 9-year OS rates.

3.4. Performance of the nomogram

The C-index values of the training and validation sets were 0.776 (0.759–0.793) and 0.766 (0.739–0.792), respectively. There was excellent agreement between the actual prediction curve and the validation curve (Fig. 3). Moreover, the actual observation and prediction values of the present nomogram exhibited good consistency in both the training and validation sets.

4. Discussion

The 2016 World Health Organization (WHO) classification for tumors of the central nervous system includes tumor histology, grade, and molecular markers.[20] Anaplastic WHO grade III gliomas are separated into 2 main subtypes among several categories: AA IDH-mutant, IDH wildtype, "Not Otherwise Specified" (NOS), AO IDH-mutant, and combined 1p/19q codeletion.[21] Although the 2016 WHO classification is the most widely used system for prognostic estimates and clinical treatments of patients with AG, it provides limited information regarding demographic data, therapeutic modalities, and tumor characteristics. Thus, the present study aimed to develop a clinical

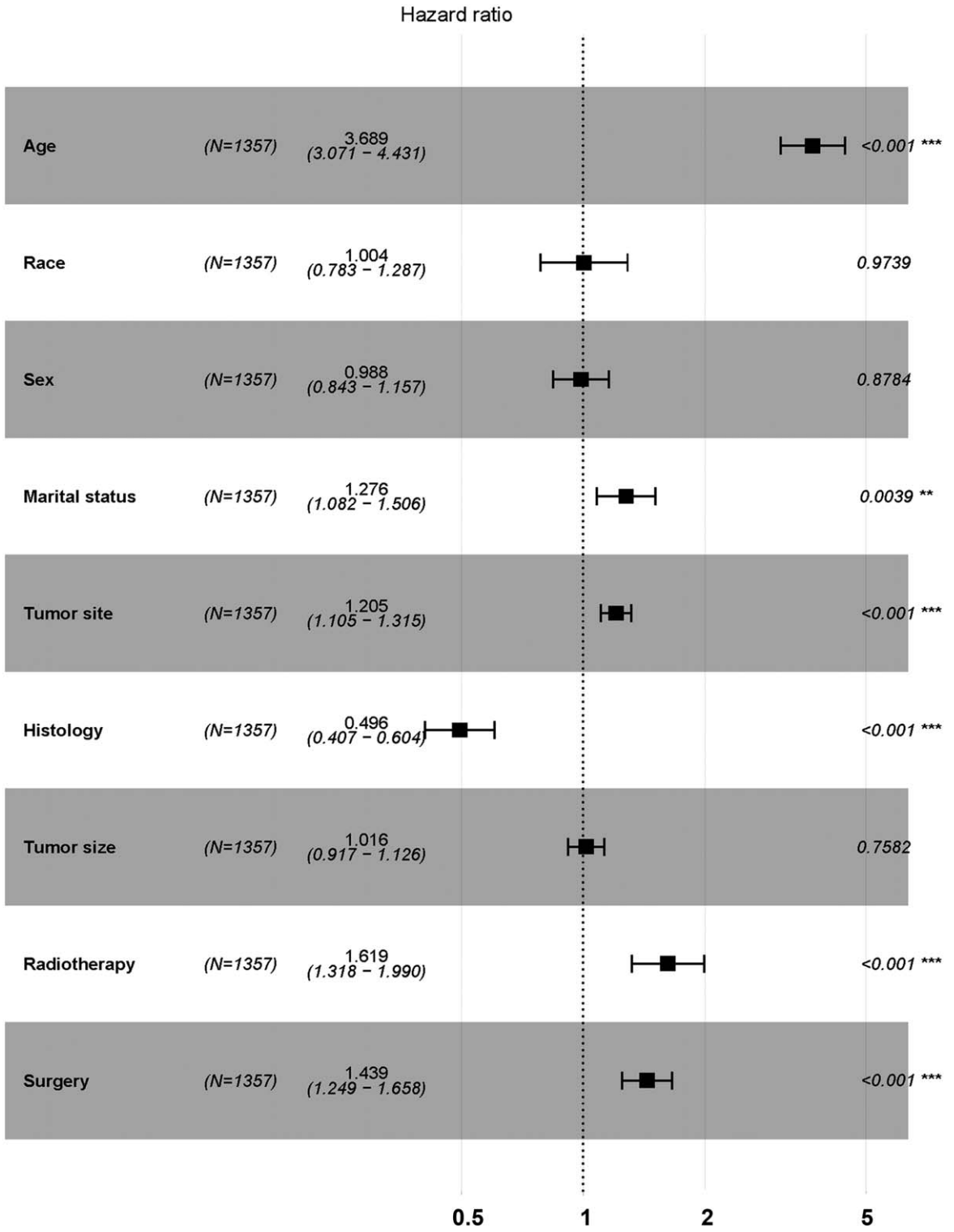

Figure 1. The constitution of the multi-variable cox model demonstrated as a forest plot. Six independent prognostic factors for patients with cerebral anaplastic glioma.

nomogram that improves upon the 2016 WHO classification system to better predict the prognostic features of AG based on individual tumor characteristics, demographic data, and therapeutic modalities.

A nomogram is a score graphic that is used as a statistical prediction model and, as an important part of modern medical decision-making, can be used to calculate the probability of survival according to individual patient characteristics.[22] In the

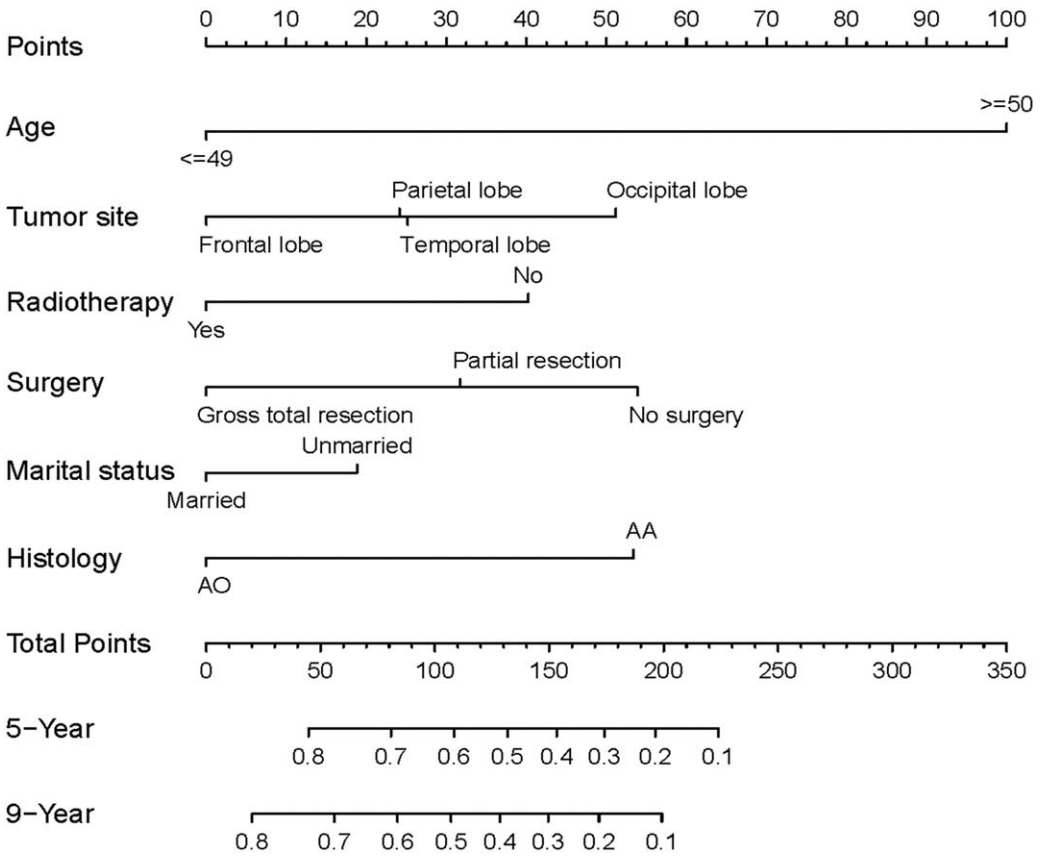

Figure 2. Nomogram for predicting 5-year and 9-year overall survival.

present study, a multivariate Cox regression analysis revealed that age, tumor site, marital status, histology, radiotherapy, and surgery were independent prognostic factors of OS in AG patients. Ultimately, a clinical nomogram was constructed for predicting AG survival based on these 6 independent prognostic factors.

The nomogram developed in this study showed that age had the largest contribution to the prognosis of AG such that being 49 years of age or younger was favorable; this may be related to the IDH mutation. An older age is associated with a lower frequency of IDH1 mutations[23,24] whereas the presence of IDH1 mutations is a strong indicator of a favorable prognosis in AA and AO patients.[25–28] Additionally, the Spanish Society of Medical Oncology clinical guidelines for AG state that being younger than 50 years of age is associated with a better prognosis.[10] Tumor location is also highly correlated with patient prognosis.[29] For example, the frequency of IDH1 mutations in the frontal lobe is higher than in other cerebral lobes[30–32] and the frequency of the IDH mutation and 1p19q codeletion in temporal tumors is lower than in other lobes among patients with cerebral AG.[33] In the present study, frontal lobe patients had the best prognosis whereas temporal lobe patients had a worse prognosis than frontal lobe and parietal lobe patients; this may have been due to the abovementioned reasons. However, occipital lobe patients had the worst prognosis in the present study but the reasons for this remain unclear. Maximal "safe" resection and radiotherapy are the mainstay treatments for AG patients[34–36] but the present study also showed that gross total resection and radiotherapy can benefit the prognosis of AG patients.

It is necessary to evaluate the discrimination and calibration capabilities of a nomogram to ensure its wide and accurate application. The C-index is used to evaluate discrimination ability while the calibration capability is evaluated by comparing the consistency of the calibration curve of the nomogram with the actual observation curve. In the present study, the nomogram had a strong discriminating ability as shown by the C-index values of the training and validation sets, which were 0.776 (0.759–0.793) and 0.766 (0.739–0.792), respectively. In both the training and validation sets, the calibration curve had good consistency with the actual observation curve and, thus, was indicative of the ideal reliability and repeatability of the nomogram.

The present study also had several limitations that should be considered. First, the SEER data has inherent limitations. For example, the AG diagnosis was based on the postoperative pathological diagnosis and, therefore, there was selection bias in terms of undergoing surgery. Furthermore, in the 2016 WHO classification, molecular markers play an important role in the prognosis of AG. However, the SEER database does not yet provide information on molecular markers, KPS scores, or chemotherapy. In the future, these 3 variables should be included to improve the nomogram. Second, the present nomogram will require validation using other independent patient groups.

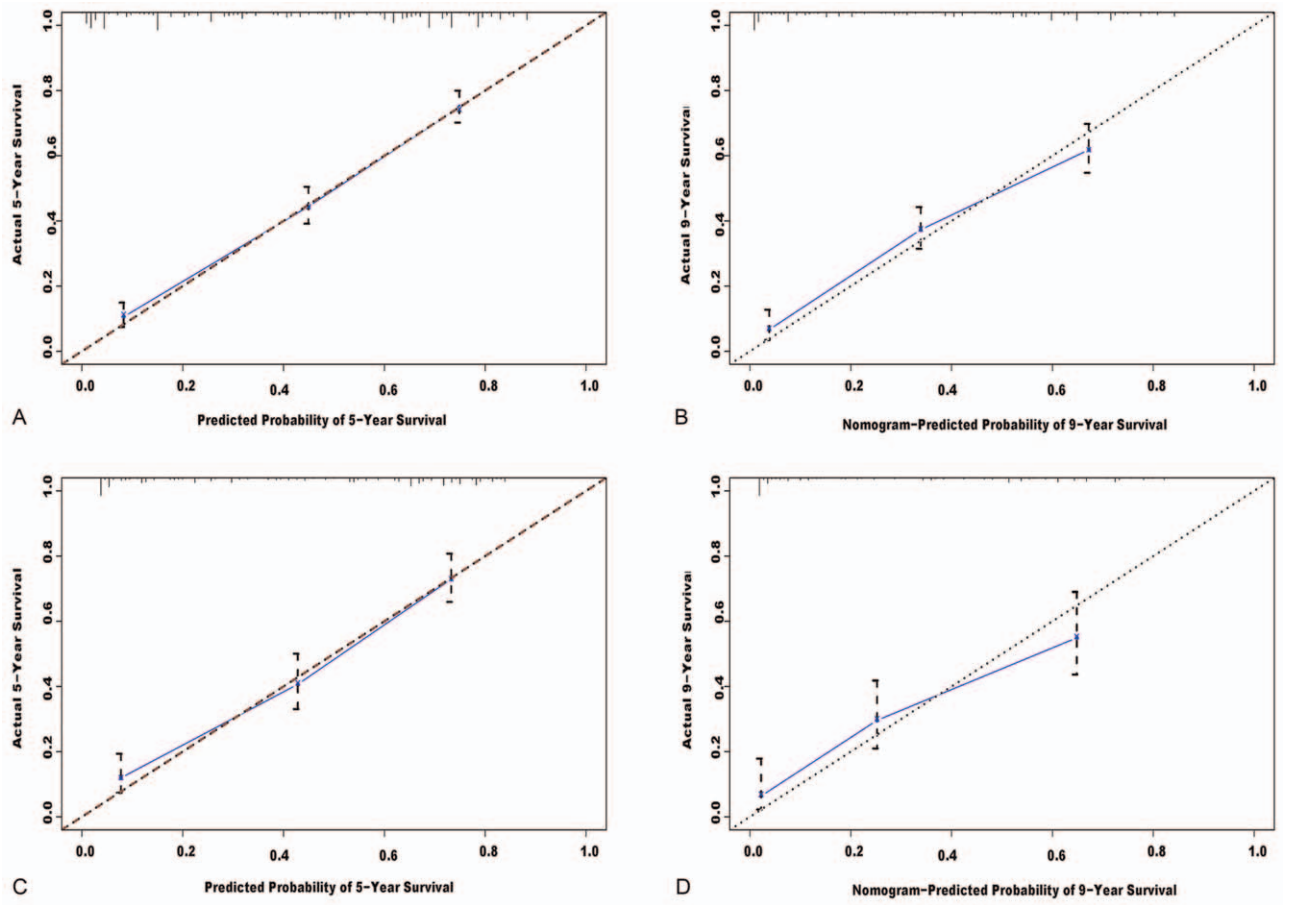

Figure 3. Calibration curves of this nomogram model: (1) training sets curves: (A) 5-Year and (B) 9-year overall survival (OS) nomogram calibration curves; (2) validation sets curves: (C) 5-Year and (D) 9-year overall survival (OS) nomogram calibration curves.

5. Conclusions

In conclusion, the 2016 WHO classification system, which is based on tumor histology, tumor grade, and molecular markers, is the current standard for guiding the treatment and prognosis of central nervous system tumors. The present study developed a novel and easy-to-use nomogram for predicting the OS of AG patients to provide a clear prognosis. In combination with the 2016 WHO classification system, this clinical nomogram can aid clinicians when making individualized predictions of AG patient survival and also improve decision-making about treatment strategies.

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Author contributions

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Methodology: Qin-Si Wan.
Supervision: Mei-Hua Li.
Writing – original draft: Ye-Yu Zhao.
Writing – review & editing: Mei-Hua Li.

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