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A nomogram with Ki-67 in the prediction of postoperative recurrence and death for glioma

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This study examined to evaluate the predictive value of a nomogram with Ki-67 in overall and disease-free survival in glioma patients, a total of 76 patients diagnosed with glioma by pathology in Tengzhou Central People's Hospital were enrolled. The baseline data and follow ups were retrospectively collected from medical records. The associations between Ki-67 and survival status were examined using log-rank test, univariate and multivariate Cox proportional hazard regression models. Calibrations were performed to validate the established nomograms. Ki-67 negative group showed of a longer OS survival time and a longer PFS survival time with log-rank test ($x^2 = 16.101$, $P < 0.001$ and $x^2 = 16.961$, $P < 0.001$). Age older than 50 years (HR = 2.074, 95% CI 1.097–3.923), abnormal treatment (HR = 2.932, 95% CI 1.343–6.403) and Ki-67 positive (HR = 2.722, 95% CI 1.097–6.755) were the independent predictive factors of death. High grade pathology (HR = 2.453, 95% CI 1.010–5.956) and Ki-67 positive (HR = 2.200, 95% CI 1.043–4.639) were the independent predictive factors of recurrence. The C-index for the nomogram of OS and PFS were 0.745 and 0.723, respectively. The calibration results showed that the nomogram could predict the overall and disease-free 1-year survival of glioma patients. In conclusion, the nomograms with Ki-67 as independent risk factor for OS and PFS could provide clinical consultation in the treatment and follow-up of malignant glioma.

Keywords Nomogram, Glioma, Ki-67, Death, Recurrence

Glioma is a common malignant tumor originating from the central nervous system, with a growing trend[1,2]. The age-adjusted average annual incidence rate of glioma was 6.42 per 100,000 population[2]. Gliomas are classified into low-grade gliomas and high-grade gliomas, which are correlated to the prognosis and used to predict a response to therapy and outcome. The standard therapy includes surgical resection when feasible, radiotherapy, and chemotherapy, but gliomas are prone to recurrence after surgery with short survival time[2,3].

Due to the high recurrence and high invasiveness of glioma, it is necessary to explore appropriate diagnostic methods for the prognosis of gliomas[4,5]. Ki-67 is a nuclear protein located in the nucleus of proliferating cells. It is closely related to the cell cycle and can affect the mitosis of cells[6–8]. Ki-67 was first applied to the classification and prognosis of breast malignant tumors, and gradually applied to central nervous system tumors[9,10].

It is closely related to the synthesis and metabolism of tumor cells in the proliferation cycle, and its appearance can confirm that the cells are in the division phase[11,12]. Ki-67 proliferation index is more accurate in counting, as a result, its expression can monitor the degree of tumor cell proliferation, the different states of the cell cycle and the rate of tumor cell proliferation. It can be used as a specific index of tumor proliferation, and reflect the malignancy of tumor tissue and judge the prognosis of patients[13].

In this study, we constructed the prognostic model of Ki-67 in glioma, which could provide a scientific basis for the diagnosis and treatment of the disease.

Methods and materials

Population and inclusion/exclusion criteria

Patients diagnosed with glioma between 2014 to 2019 in Neurosurgery Department, Tengzhou Central People's Hospital was enrolled. The baseline data including admission ID, age, gender, marriage, BMI, scales, tumor length and width, epilepsy, pathology, treatment, and followups was retrospectively collected. The length and width of glioma was measured in the maximum cross-sectional area in T2/FLAIR high-intensity lesions of MRI

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imaging. Patients who received surgery and concurrent postoperative chemoradiation were included. Patients without pathology diagnosis or chemoradiation were excluded. Patients were followed every month for the first year. After the first year, patients were followed every three months. Patients lost to follow-up or survived at the time of last follow-up time were regarded as censored. This study was approved by the Ethics Committee of Tengzhou Central People's Hospital (Approval No. 2020-31). Baseline data collection from the medical records was conducted in compliance with the declaration of Helsinki. Informed consents were waived.

Ki-67 testing

Ki-67 is a sensitive marker of cell proliferation and positively associated with the malignant degree of glioma[14]. Up to date, Ki-67 is widely used in pathology to evaluate cell proliferation in malignancies, yet the relationship between Ki-67 and prognosis of glioma remains largely unknown[15]. The surgically excised glioma tissue was formalin-fixed, paraffin-embedded, and sectioned for pathological diagnosis. The tissue was read by qualified pathologists after the immunohistochemical staining test (detection kit from Maixin Biotechnology Development Co., Ltd) under the 10–40 × high-power microscope. A total of five fields of view were randomly selected to count the staining results of 1000 tumor cells. Positive staining results were defined as yellow staining on the nuclei of glioma cells in tissue sections, positive cells > 10%, [16–18] and no background staining.

Glasgow coma scale

The glasgow coma scale (GCS) is a well-established neurological tool designed to assess the patient's level of consciousness after brain injury in clinical practice[19]. The scale evaluates the patient's best eye response, best verbal response, and best motor response, and then assigns a score that ranges from three to fifteen. This scale is the main method in use for assessment of head injuries[20].

Karnofsky performance scale

The karnofsky performance scale (KPS) is one of the most commonly used scale to assess patients' quality of life and is used to evaluate condition and ability to undergo chemotherapy in glioma patients[21]. A score between 0 and 100 is assigned by a health professional after watching a patient perform common tasks. Decreasing numbers mean that the patient has less ability to perform activities of daily living. The higher score associated with better health status, which reflecting the higher tolerance to the adverse effects of treatment.

Pathology grade

The pathology grade of the patients was classified by the grading system developed by the world health organization (WHO)[22]. According to this grading system, gliomas are classified into grades 1 (least malignant, best prognosis) to grade 4 (most malignant, worst prognosis). Gliomas can be further classified according to the pathological malignancy of tumor cells: low-grade gliomas (WHO grades 1–2) and high-grade gliomas (WHO grades 3–4).

Patient and public involvement

In a retrospective analysis of an anonymous hospital inpatient database, no public or patient participation was involved.

Statistical analysis

Continuous variables were described using median (range) and compared with Mann–Whitney test. Categorical variables were described using frequency (percentage) and compared using chi-square test. The survival curves were plotted using the Kaplan–Meier method, and log-rank test was used for statistical analysis. The associations between Ki-67 and survival status were examined using univariate and multivariate Cox proportional hazard regression models. Univariate Cox proportional hazard analysis was performed to identify risk factors of death and recurrence and Hazard Ratio (HR) with 95% Confidence Interval (95% CI) of potential risk factors was displayed. Multivariate Cox proportional hazard regression analysis was used to select independent influence factors and nomograms were built based mainly on these results. Harrell's concordance index (C-index) was used to assess the reliability of the nomogram. Calibration for the established nomograms were performed and 1000 repetitions of bootstrap sample corrections were applied to internally validate the nomograms. All statistical tests were two-sided using a 0.05 significance level. The data analyses and nomograms were performed using R software version 3.4.3.

Results

Descriptive analysis of the patient population

Overall, 76 patients were included in the final data analysis (Table 1). In total, there were 44.74% of the patients under the age of 50 years old, while 55.26% of the patients were older than 50 years old. Males accounted for 57.89% of the total patients. The median BMI was 23.70 (12.40–29.37) kg/m^2. The median GCS and KPS scores were 15.00 (3.00–15.00) and 90.00 (10.00–100.00), respectively. The median tumor length and width were 5.20 (1.20–8.00) cm and 3.90 (1.00–5.70) cm, respectively. The pathology grades were 26.32% of low grade and 73.68% of high grade. Only 32.89% of glioma patients received normal treatment.

A total of 32 patients were Ki-67 negative (Ki-67 ≤ 10%) and 44 patients were Ki-67 positive (Ki-67 > 10%). The females in Ki-67 negative group accounted higher percentage than in Ki-67 positive group (P = 0.033). The pathology grades in Ki-67 negative group were lower than in Ki-67 positive group (P < 0.001). Other demographic and clinical characteristics showed no significance in the two groups.

Characteristics		Total (n = 76)	Ki67 negative (Ki67 < = 10%) (n = 32)	Ki67 positive (Ki67 > 10%)(n = 44)	P
Age (years)	≤ 50	34 (44.74)	16 (50.0)	18 (40.91)	0.431
	> 50	42 (55.26)	16 (50.0)	26 (59.09)	
Gender	Female	32 (42.11)	18 (56.25)	14 (31.82)	0.033
	Male	44 (57.89)	14 (43.75)	30 (68.18)	
Marriage*	No	7 (9.21)	2 (6.25)	5 (11.36)	0.692
	Yes	69 (90.79)	30 (93.75)	39 (88.64)	
BMI		23.70 (12.40–29.37)	23.78 (17.93–29.37)	23.43 (12.40–26.17)	0.542
GCS score		15.00 (3.00–15.00)	15.00 (3.00–15.00)	15.00 (11.00–15.00)	0.886
KPS score		90.00 (10.00–100.00)	90.00 (10.00–100.00)	90.00 (10.00–90.00)	0.745
Tumor length (cm)		5.20 (1.20–8.00)	4.75 (1.70–8.00)	5.65 (1.20–8.00)	0.103
Tumor width (cm)		3.90 (1.00–5.70)	3.60 (1.10–5.70)	4.20 (1.00–5.00)	0.199
Epilepsy*	No	66 (86.84)	24 (75.00)	42 (95.45)	0.014
	Yes	10 (13.16)	8 (25.00)	2 (4.55)	
Pathology	Low grade	20 (26.32)	19 (59.38)	1 (2.27)	< 0.001
	High grade	56 (73.68)	13 (40.63)	43 (97.73)	
Normal treatment	Yes	25 (32.89)	12 (37.50)	13 (29.55)	0.466
	No	51 (67.11)	20 (62.50)	31 (70.45)	

Table 1. Demographic characteristics of the enrolled patients.

Ki-67 and other risk factors of death and recurrence in glioma

The median overall survival (OS) time was 28.9 months in Ki-67 negative group, and 8.1 months in Ki-67 positive group (Fig. 1A). The median progression-free survival (PFS) time was 18.1 months in Ki-67 negative group, and 5.2 months in Ki-67 positive group (Fig. 1B). In the OS and PFS curves, Ki-67 negative group showed of a longer OS survival time and a longer PFS survival time with log-rank test ($x^2 = 16.101$, $P < 0.001$ and $x^2 = 16.961$, $P < 0.001$).

In the univariate Cox regression model of death (Table 2), age older than 50 years, high grade pathology, abnormal treatment and Ki-67 positive were the risk factors of death in glioma patients (all $P < 0.05$). In the multivariate analysis, age older than 50 years (HR = 2.074, 95% CI 1.097–3.923), abnormal treatment (HR = 2.932, 95% CI 1.343–6.403) and Ki-67 positive (HR = 2.722, 95% CI 1.097–6.755) were the independent predictive factors of death in glioma patients ($P = 0.025$, 0.007 and 0.032, respectively).

In the univariate Cox regression model of recurrence (Table 3), high grade pathology and Ki-67 positive were the risk factors of recurrence in glioma patients (both $P < 0.001$). In the multivariate analysis, high grade pathology (HR = 2.453, 95% CI 1.010–5.956) and Ki-67 positive (HR = 2.200, 95% CI 1.043–4.639) were the independent predictive factors of recurrence in glioma patients ($P = 0.047$ and 0.038, respectively).

A nomogram for the prediction of death and recurrence in glioma patients

In combination of the risk factors of death and recurrence, the risk factors of age, Ki-67, pathology grade and treatment were used to develop predictive nomograms for the glioma patients.

For each patient, points were assigned for each of these demographic and clinical factors (age, Ki-67, pathology, and treatment), then a total score and a corresponding 1-year, 2-year and 3-year predicted the probability of OS and PFS were calculated from the nomograms (Fig. 2 (Figs. 2, 3) Fig. 3). The C-index for the nomogram of OS was 0.745, while the C-index for the nomogram of PFS was 0.723. All calibration plots for the probability of OS and PFS fit well. The calibration results showed that the nomogram could predict the overall and disease-free 1-year survival of glioma patients.

Discussion

As a risk prediction and assessment tool, nomogram has broadly used in clinical interpretation, and have been widely adopted in prognostic models[23–25]. However, it is rarely used in the prognosis of glioma patients[26,27]. In this study, we established a nomogram-based method to predict the OS and PFS. The nomogram exhibited the ability to predict the OS and PFS according to the calibration curves.

In this study, the nomogram consisted of four prognostic factors according to the multivariate Cox regression model. Age, Ki-67 expression level, pathology grade and treatment were included in both the nomogram of OS and PFS. Older age, higher Ki-67 expression, higher pathology grade and abnormal treatment were associated with poor survival in glioma patients.

Generally, one of the common risk factors for cancer was ageing[28–30]. Age was associated with OS in the Cox regression nomogram in this study. Almost half of the patients enrolled in this study were under 50 years old. A study from the cancer genome atlas (TCGA) dataset also showed that age at initial pathologic diagnosis was most associated with the overall survival of LGG patients ($P < 0.001$ and HR = 19.8), which might be caused by the profiles of genomic alterations[31]. In addition, other host-derived factors, such as age-related immune alterations, might play an important role in the poor prognosis observed in these patients[32].

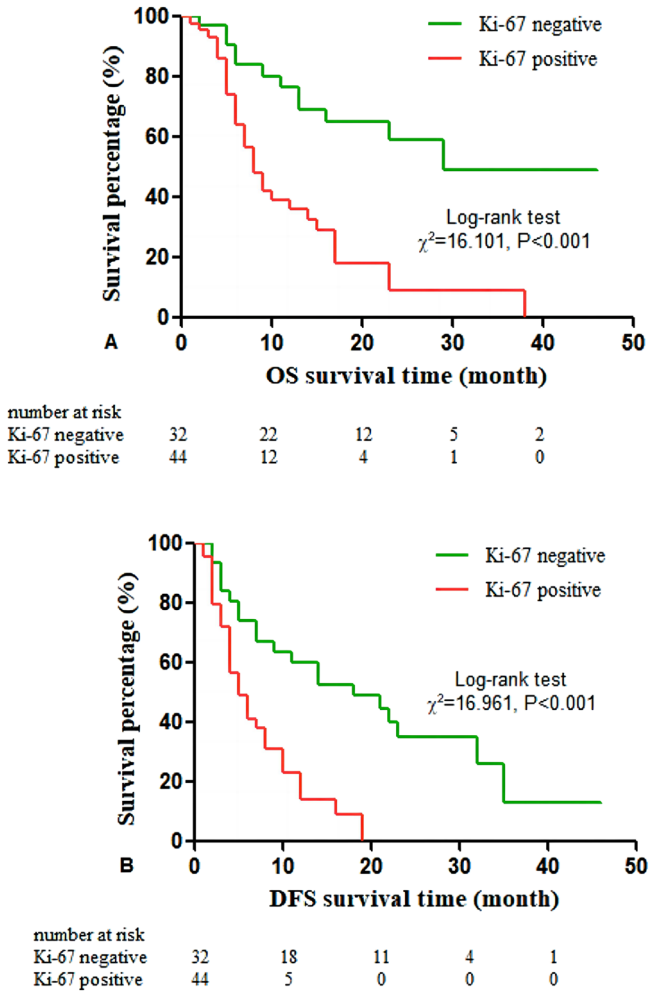


Fig. 1. The overall all survival (**A**) and progression-free survival (**B**) curves between Ki-67 negative and Ki-67 positive.

Previous studies showed that histological subtype was one of the most important prognostic factors of WHO grade 3 gliomas. Surgery, chemotherapy, and radiotherapy have been the most effective glioma treatment methods up to date[33]. The consistent application of the multimodal treatment options for glioma has led in recent years to improved survival[34]. In our study, patients received normal treatment showed a longer survival time. The results prompted that the survival rate could be improved and the treatment methods played an important role in the survival of malignant gliomas.

Ki-67 was widely used as a biomarker of cell proliferation, which was associated with the pathology grade and malignant degree for glioma[35–37]. The cut-off value of Ki-67 high expression was defined as 10%, which was consistent with previous studies[38–40]. Our results showed that Ki-67 expressed significant higher in high grade glioma (Grade 3–4), which meant Ki-67 could be related to the pathology and prognosis in glioma patients. A previous study by Liu et al. showed that Ki-67 was highest in WHO grade IV tumors with statistically significance[41]. Another study by Yuan et al. also showed that the high expression rate of Ki-67 in patients with grade I-II brain glioma was significantly lower compared with patients with grade III-IV glioma[42]. These consistent results showed that Ki-67 might be a potential biomarker in the prognostic of glioma.

One the other hand, the studies on Ki-67 as a prognostic marker has been limited, especially in the prognosis of recurrence in glioma patients. A retrospective study showed that high Ki-67 expression were significantly

Characteristics		Univariate Cox regression			Multivariate Cox regression		
		HR	95% CI	P	HR	95% CI	P
Age	≤ 50 years	1			1		
	> 50 years	1.900	1.025–3.524	0.042	2.074	1.097–3.923	0.025
Gender	Female	1					
	Male	1.065	0.583–1.946	0.837			
Marriage	No	1					
	Yes	1.166	0.414–3.284	0.771			
BMI	< 24	1					
	≥ 24	1.169	0.645–2.119	0.606			
GCS score	15	1					
	< 15	0.834	0.328–2.120	0.703			
KPS score	≥ 90	1					
	< 90	1.096	0.525–2.289	0.807			
Tumor length	< 5 cm	1					
	≥ 5 cm	1.243	0.687–2.250	0.472			
Tumor width	< 4 cm	1					
	≥ 4 cm	1.24	0.681–2.259	0.482			
Epilepsy	No	1					
	Yes	0.444	0.158–1.250	0.124			
Pathology	Low grade	1			1		
	High grade	4.126	1.792–9.497	< 0.001	1.999	0.668–5.984	0.216
Normal treatment	Yes	1			1		
	No	2.788	1.290–6.027	0.009	2.932	1.343–6.403	0.007
Ki-67	Negative (≤ 10%)	1			1		
	Positive (> 10%)	3.791	1.898–7.572	< 0.001	2.722	1.097–6.755	0.031

Table 2. The Cox proportion hazard regression on the death risk of brain glioma.

associated with OS in multivariate Cox analyses with HR = 3.40 (1.64–7.02) in low-grade glioma, but not significantly associated with PFS (HR = 1.607 (0.93–2.77), P = 0.09). In anaplastic gliomas and glioblastomas, high Ki-67 expression were significantly associated with PFS in multivariate Cox analyses with HR = 1.25 (1.01–1.54), but not significantly associated with OS (HR = 1.09 (0.85–1.39), P = 0.49)[43]. In our study, the results showed that the high expression of Ki-67 were both significant in OS and PFS in glioma patients, with the HR of 2.722 (95% CI 1.097–6.755) and 2.200 (95% CI 1.043–4.639). The results showed that Ki-67 potentially associated with the prognosis of glioma.

There are also some limitations in our nomogram-based model. The limited sample size and single center dataset would bring bias in the credibility of the risk prediction model. Up to date, our nomogram considered Ki-67 as a molecular marker in the prediction of survival and recurrence in glioma, which would help improve the nomogram built by Zhao et al. previously[26]. A more detailed pathology classification should be considered in the future in a large sample size multicenter study when the nomogram would be further improved.

And depending on the institution's capabilities or facilities, IDH mutation could not be checked. It is now an era in which glioma research especially in high-grade gliomas cannot be talked about except for molecular diagnosis. The lack of analytical diagnostic data makes our nomogram less reliable. As our technological capabilities continue to improve in the future, the subsequent studies on glioma will be distinguished from the presence or absence of IDH mutation.

Conclusion

The study provided a predictive tool with Ki-67 in glioma patients. The nomograms for OS and PFS could provide clinical consultation in the treatment and follow-up of malignant glioma.

Characteristics		Univariate Cox regression			Multivariate Cox regression		
		HR	95% CI	P	HR	95% CI	P
Age	≤ 50 years	1			1		
	> 50 years	1.332	0.774–2.291	0.300	1.335	0.772–2.309	0.301
Gender	Female	1					
	Male	1.308	0.755–2.265	0.338			
Marriage	No	1					
	Yes	1.989	0.702–5.635	0.196			
BMI	< 24	1					
	≥ 24	1.319	0.772–2.254	0.311			
GCS score	15	1					
	< 15	0.615	0.261–1.449	0.266			
KPS score	≥ 90	1					
	< 90	0.964	0.494–1.879	0.914			
Tumor length	< 5 cm	1					
	≥ 5 cm	1.375	0.803–2.352	0.246			
Tumor width	< 4 cm	1					
	≥ 4 cm	1.342	0.779–2.310	0.289			
Epilepsy	No	1					
	Yes	0.523	0.222–1.235	0.139			
Pathology	Low grade	1			1		
	High grade	3.818	1.833–7.953	< 0.001	2.453	1.010–5.956	0.047
Normal treatment	Yes	1			1		
	No	1.233	0.691–2.202	0.478	1.133	0.628–2.045	0.678
Ki-67	Negative (≤ 10%)	1			1		
	Positive (> 10%)	3.604	1.894–6.857	< 0.001	2.200	1.043–4.639	0.038

Table 3. The Cox proportion hazard regression on the recurrence risk of brain glioma.

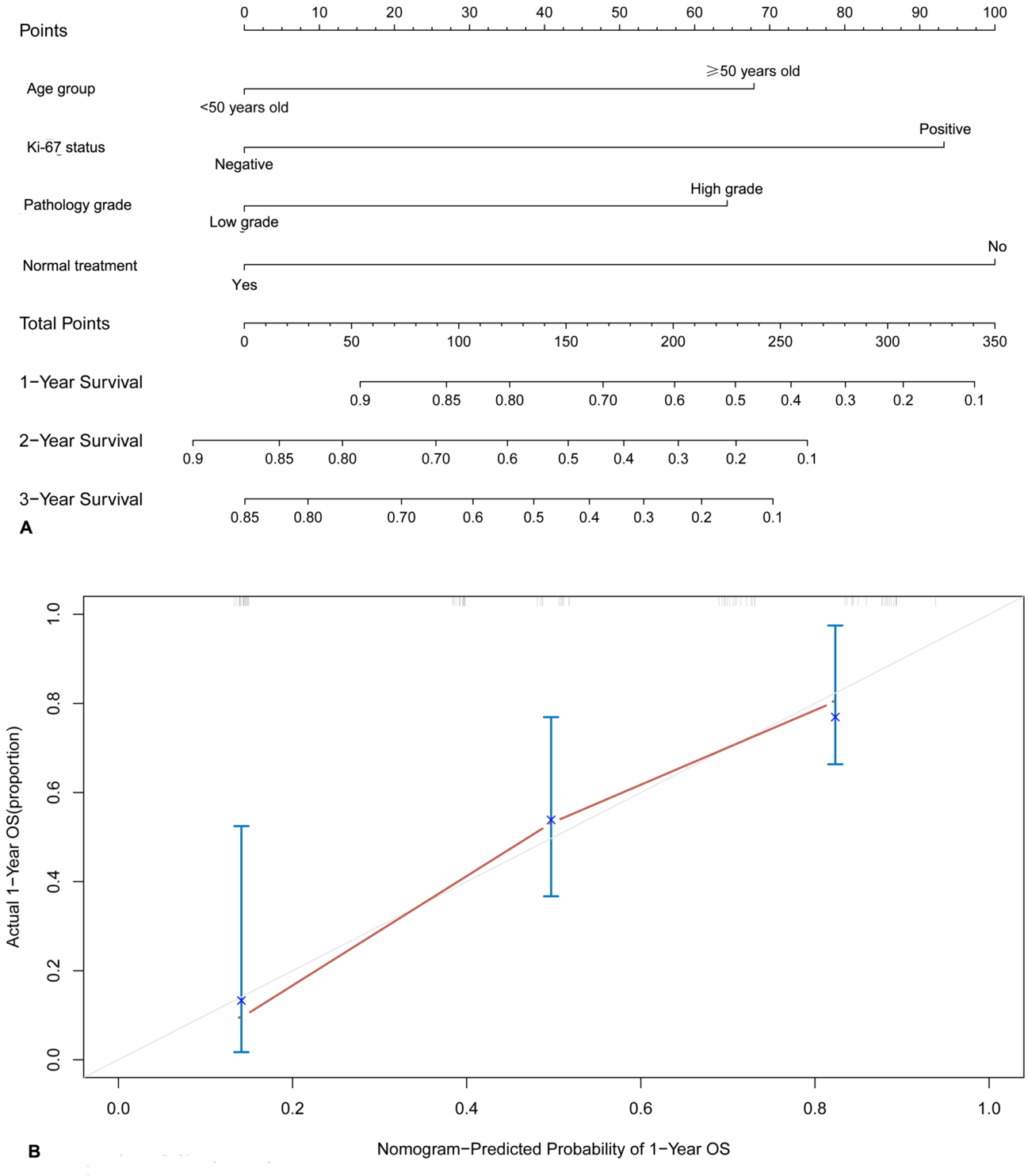
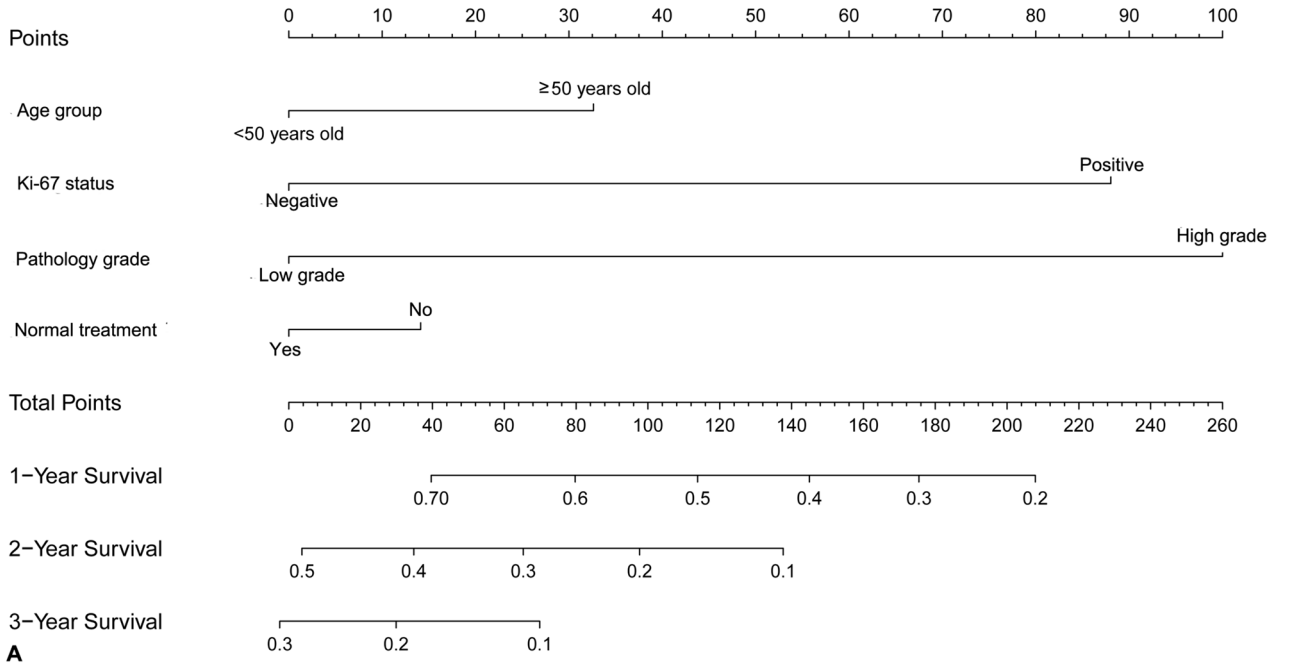


Fig. 2. The nomogram (**A**) and calibration (**B**) in the prediction of death in glioma patients.



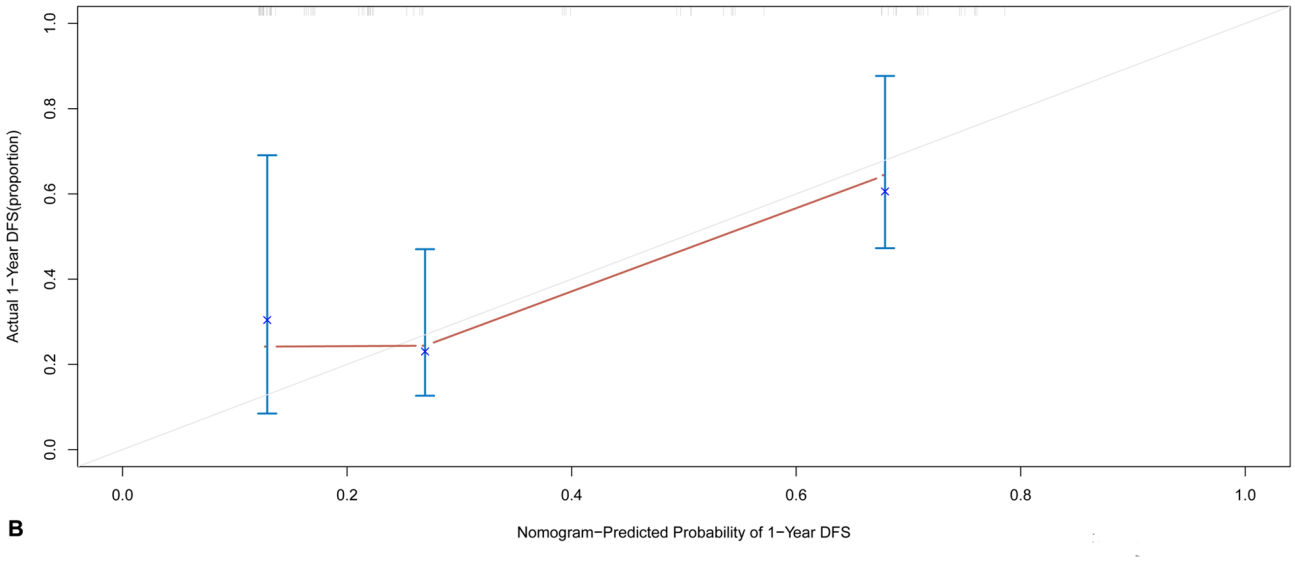


Fig. 3. The nomogram (**A**) and calibration (**B**) in the prediction of recurrence in glioma patients.

Data availability

The authors declare that all experimental data supporting this study are available from the corresponding author upon reasonable request.

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