Nomogram predicts the overall survival of patients with Glioma

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Research

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Abstract

**Aim** Our study aimed to establish a nomogram to predict the cancer-specific survival (CSS) of patients with Glioma.

**Patients and methods** Patients diagnosed with glioma between 2004 and 2016 were collected from the SEER database. On the basis of the logistic regression model, the nomogram was established, the C-index was used to evaluate the accuracy of the nomogram, and the Decision Curve Analysis was used to evaluate the clinical use of the nomogram.

**Results** 2626 eligible patients were randomly divided into training group (n=1864) and verification group (n=762). Nomogram had better discrimination ability, the C index of the training cohort was 0.74, and the C index of the verification cohort was 0.736. This new predictive model has shown better discriminative ability and greater benefits in both training and validation cohorts to predict CSS in patients with Glioma.

**Conclusion** A nomogram was constructed to predict the CSS of Glioma patients at 1, 3, and 5 years. The verification showed that the nomogram had better discrimination and calibration ability, indicating that the nomogram can be used to predict the CSS of Glioma patients and guide the treatment of Glioma patients.

1. Introduction

Glioma is a primary intracranial tumor with poor prognosis, which is highly aggressive, accounting for about 81% of malignant tumors, and has a high morbidity and mortality \[1,2\]. As the second most common primary central nervous system tumor in the world,

According to histological types, astrocytoma, glioblastoma and oligodendroglioma are clinically classified \[3–5\]. Without systematic treatment, most patients are diagnosed and die within a year. At present, surgery is still the main treatment method, combined with radiotherapy, chemotherapy, immunotherapy, etc., which can delay disease recurrence to a certain extent and prolong the survival period \[6–9\]. The prognosis of patients various with different treatment options. For clinicians, it is very important to accurately predict the CSS and choose the best treatment method. However, there is no scoring system on the relationship between clinicopathological factors and CSS in glioma patients. Therefore, the purpose of this study is to identify independent factors related to CSS and establish a nomogram to predict 1, 3, and 5 CSS of glioma patients. The 5-year CSS provides individualized survival prediction and treatment plans for glioma patients.

2. Patients And Methods

This study used the National Cancer Institute database (The Surveillance, Epidemiology, and End Results), which records the morbidity, mortality, and disease status of approximately 30% of millions of patients with malignant tumors in the United States. The SEER*Stat software version 8.3.5 was used to
extract the data of patients diagnosed with glioma from 2004 to 2016 based on the SEER database. The training cohort consisted of the following patients: the third edition of the International Classification of Diseases in Oncology (ICD-O-3). The exclusion criteria were: (1) patients without pathological diagnosis; (2) patients with missing or incomplete clinical pathological data. Because the SEER study data are publicly available, this study does not require the approval and informed consent of the institutional review committee. All authors have signed the authorization form and obtained the permission of the SEER organization to access and use the data set.

2.1 Data collection

The clinicopathological characteristics used in this study are: time at diagnosis, age at diagnosis, gender, race, Marital status, Insurance status, primary site, histological grade, summary stage, tumor size, chemotherapy, surgery for primary site and survival months.

2.2 Statistical Analysis

SPSS software version 22 and the version 3.4.2 software were used for statistical analysis. T test was used for comparison between two groups, and chi-square test was used for mandatory categorical variables. Single factor logistic regression analysis analyzes the relationship between CSS and clinicopathological factors. In multivariate analysis, variables deemed significant were further analyzed to determine independent risk factors for CSS. The HR and related 95% confidence interval (CI) were calculated, and the independent risk factors identified in the multivariate analysis were included in the Nomogram prediction method for glioma CSS prediction, and the C index and calibration curve were used to evaluate the performance of the nomograph. Decision curve analysis (DCA) was used to evaluate the clinical application of nomogram, and P < 0.05 was used as a sign of Statistical significance.

3. Results

3.1 characteristics of Glioma

A total of 2626 patients were enrolled in this study, all of whom were diagnosed as Glioma. The 2626 patients were assigned to two different cohorts, including 1864 in the training cohort (70.98%) and 762 in the verification cohort (29.02%). There was no statistical differences among variables between the training and validation groups (P > 0.05), Table 1 shows the demographic and pathological characteristics of Glioma patients. (Table 1.)
### Table 1
Clinicopathological characteristics of all patients

| Characteristics                  | Training set (n = 1864) | Validation set (n = 762) | P value |
|----------------------------------|-------------------------|--------------------------|---------|
| Year of diagnosis, n (%)         |                         |                          | 0.761   |
| 2004–2008                        | 747 (40.1)              | 305 (40.0)               |         |
| 2009–2012                        | 610 (32.7)              | 242 (31.8)               |         |
| 2013–2016                        | 507 (27.2)              | 215 (28.2)               |         |
| Age (years), n (%)               |                         |                          | 0.465   |
| <60                              | 1381 (74.1)             | 575 (75.5)               |         |
| ≥60                              | 483 (25.9)              | 187 (24.5)               |         |
| Sex, male, n (%)                 | 1045 (56.1)             | 441 (57.9)               | 0.395   |
| Race, n (%)                      |                         |                          | 0.399   |
| White                            | 1539 (82.6)             | 640 (84.0)               |         |
| Black                            | 167 (9.0)               | 63 (8.3)                 |         |
| Others                           | 158 (8.4)               | 59 (7.7)                 |         |
| Marital status at diagnosis, n (%)|                         |                          | 0.556   |
| Married                          | 862 (46.2)              | 362 (47.5)               |         |
| No/unknown                       | 1002 (53.8)             | 400 (52.5)               |         |
| Insurance status, n (%)          |                         |                          | 0.168   |
| Insured                          | 1363 (73.1)             | 537 (70.5)               |         |
| No/unknown                       | 501 (26.9)              | 225 (29.5)               |         |
| Primary site, n (%)              |                         |                          | 0.465   |
| Cerebrum                         | 92 (4.9)                | 34 (4.5)                 |         |
| Frontal lobe                     | 489 (26.2)              | 212 (27.8)               |         |
| Temporal lobe                    | 237 (12.7)              | 99 (13.0)                |         |
| Parietal lobe                    | 141 (7.6)               | 63 (8.3)                 |         |
| Occipital lobe                   | 34 (1.8)                | 8 (1.0)                  |         |
| Ventricle, NOS                   | 10 (0.5)                | 10 (1.3)                 |         |
| Cerebellum, NOS                  | 32 (1.7)                | 10 (1.3)                 |         |

C-index for CSS in test set 0.740 95%CI (0.717–0.763); in validation set 0.736 95%CI (0.701–0.771)
| Characteristics                        | Training set (n = 1864) | Validation set (n = 762) | P value |
|---------------------------------------|-------------------------|--------------------------|---------|
| Brain stem                            | 561 (30.1)              | 223 (29.3)               |         |
| Overlapping lesion of brain           | 181 (9.7)               | 63 (8.3)                 |         |
| Brain, NOS                            | 87 (4.8)                | 40 (5.2)                 |         |
| Histological grade, n (%)             |                         |                          | 0.697   |
| Well differentiated                   | 1102 (59.1)             | 464 (60.9)               |         |
| Moderately differentiated             | 163 (8.7)               | 53 (7.0)                 |         |
| Poorly differentiated                 | 139 (7.5)               | 60 (7.9)                 |         |
| Undifferentiated                     | 460 (24.7)              | 185 (24.3)               |         |
| Summary stage, n (%)                  |                         |                          | 0.171   |
| Localized                             | 1519 (81.5)             | 643 (84.4)               |         |
| Regional                              | 326 (17.5)              | 108 (14.2)               |         |
| Distant                               | 19 (1.0)                | 11 (1.4)                 |         |
| Tumor size, n (%)                     |                         |                          | 0.227   |
| <3cm                                  | 862 (46.2)              | 327 (42.9)               |         |
| 3-5cm                                 | 537 (28.8)              | 238 (31.2)               |         |
| ≥5cm                                  | 465 (24.9)              | 197 (25.9)               |         |
| Chemotherapy, n (%)                   |                         |                          | 0.316   |
| Yes                                   | 1217 (65.3)             | 474 (62.2)               |         |
| No/unknown                            | 647 (34.7)              | 1288 (37.8)              |         |
| Surgery for primary site, n (%)       |                         |                          | 0.340   |
| Yes                                   | 928 (49.8)              | 395 (51.8)               |         |
| No/unknown                            | 936 (50.2)              | 367 (48.2)               |         |
| Survival months                       | 17.0 (7.0, 49.0)        | 17.0 (8.0, 46.0)         | 0.516   |
| OS, n (%)                             | 1236 (66.3)             | 482 (36.7)               | 0.135   |
| CSS, n (%)                            | 1003 (53.8)             | 402 (52.8)               | 0.624   |

C-index for CSS in test set 0.740 95%CI (0.717–0.763); in validation set 0.736 95%CI (0.701–0.771)

3.2 Independent prognostic factors in the training set
Single factor analysis screened risk factors, and all these factors entered multivariate logistic regression analysis. The single factor results of CSS indicate that age > 60 years old, married (P < 0.001), frontal lobe (P < 0.001), distant summary stage (P < 0.001), tumor size > 3cm (P < 0.001), surgery (P < 0.001) patients are more likely to have a higher mortality rate. Multivariate analysis of CSS showed that age > 60 years old, married (P = 0.025), frontal lobe (P = 0.001), Temporal lobe (P = 0.043), regional (P < 0.001), distant (P = 0.008), surgery Of patients have a higher risk of death (Table 2).
|                          | Univariate analysis | Multivariate analysis |
|--------------------------|---------------------|-----------------------|
|                          | HR (95%CI)          | P                     | HR (95%CI)          | P                     |
| Age (years)              |                     |                       |                      |                       |
| ≥60                      | 1.35 (0.86–2.13)    | 0.190                 |                      |                       |
| <60                      | Ref.                | -                     |                      |                       |
| Sex, male                | 1.31 (0.81–2.09)    | 0.269                 |                      |                       |
| Primary site             |                     |                       |                      |                       |
| Left colon               | 1.48 (0.88–2.49)    | 0.140                 |                      |                       |
| Right colon              | 1.67 (0.94–2.95)    | 0.078                 |                      |                       |
| Rectum                   | Ref.                | -                     |                      |                       |
| Family history of cancer | 7.14 (0.98–51.35)   | 0.054                 |                      |                       |
| Histological grade       |                     |                       |                      |                       |
| Well differentiated      | Ref.                | -                     |                      |                       |
| Moderately differentiated | 1.14 (0.60–2.18)   | 0.683                 |                      |                       |
| Poorly differentiated    | 2.04 (0.84–4.92)    | 0.114                 |                      |                       |
| Tumor size               |                     |                       |                      |                       |
| <2cm                     | Ref.                | -                     |                      |                       |
| 2-5cm                    | 1.14 (0.35–3.69)    | 0.824                 |                      |                       |
| ≥5cm                     | 1.45 (0.44–4.73)    | 0.540                 |                      |                       |
| Vascular invasion        |                     |                       |                      |                       |
| Yes                      | 1.13 (0.63–2.03)    | 0.671                 |                      |                       |
| No                       | Ref.                | -                     |                      |                       |
| Circumferential resection margin |             |                       |                      |                       |
| Yes                      | 1.42 (0.23–10.08)   | 0.653                 |                      |                       |
| No                       | Ref.                | -                     |                      |                       |
| T stage                  |                     |                       |                      |                       |
| T1                       | Ref.                | -                     | Ref.                | -                     |
| T2                       | 1.54 (0.038–6.53)   | 0.556                 | 1.60 (0.34–7.44)    | 0.549                 |
|                  | Univariate analysis |             | Multivariate analysis |             |
|------------------|---------------------|-------------|-----------------------|-------------|
|                  | HR (95%CI)          | P           | HR (95%CI)            | P           |
| T3               | 1.67 (0.37–7.62)    | 0.510       | 1.17 (0.26–5.19)      | 0.836       |
| T4               | 7.17 (1.73–29.65)   | 0.007       | 3.92 (1.03–16.91)     | 0.038       |
| N stage          |                     |             |                       |             |
| N0               | Ref.                | -           | Ref.                  | -           |
| N1               | 0.68 (0.31–1.53)    | 0.234       | 0.64 (0.25–1.61)      | 0.344       |
| N2               | 1.56 (0.72–3.43)    | 0.125       | 0.58 (0.20–1.69)      | 0.320       |
| N3               | 2.70 (1.15–5.88)    | 0.010       | 0.78 (0.26–2.32)      | 0.655       |
| TNM stage        |                     |             |                       |             |
| Stage I          | Ref.                | -           | Ref.                  | -           |
| Stage II         | 1.59 (0.54–4.73)    | 0.403       | 1.12 (0.32–3.93)      | 0.862       |
| Stage III        | 4.96 (1.80–13.69)   | 0.002       | 3.05 (1.07–10.67)     | 0.040       |
| Adjuvant chemotherapy |                 |             |                       |             |
| Yes              | 0.66 (0.16–2.71)    | 0.569       |                       |             |
| No               | Ref.                | -           | Ref.                  | -           |
| Radiotherapy     |                     |             |                       |             |
| Yes              | 0.46 (0.28–0.76)    | 0.002       | 0.71 (0.40–1.25)      | 0.231       |
| No               | Ref.                | -           | Ref.                  | -           |
| CSII             |                     |             |                       |             |
| Low              | Ref.                | -           | Ref.                  | -           |
| Intermediate     | 4.62 (2.03–10.54)   | < 0.001     | 3.37 (1.53–7.43)      | 0.003       |
| High             | 15.62 (6.95–35.08)  | < 0.001     | 10.11 (4.64–22.03)    | < 0.001     |

### 3.3 Construction and verification of survival line graph

Based on the CSS-based multivariate COX results (Table 2), age, marital status, grade, primary site, surgery and summary stage are finally included in the nomogram. Patients’ 1-, 3-, and 5-year overall survival predictions were estimated by calculating a weighted total score for each variable (Fig. 1). The performance of the Nomogram has been verified internally through discrimination and calibration methods. The C index of the training set is 0.74 (95% CI: 0.717–0.763), and the C index of the validation
set is 0.736 (95% CI: 0.701–0.771), indicating that the nomogram has better discrimination ability. The calibration chart shows a good correlation between the observed operating system and the nomogram predicted operating system (Fig. 2).

3.4 Clinical application of the model
Decision curve analysis (DCA) mainly evaluates predictive models from the perspective of clinical consequences. When the score is 0–1, patients can obtain a greater net benefit by using the Nomograph to predict glioma survival (Fig. 3).

3.5 The overall survival of the nomogram with different score
The patients were divided into three groups according to the scores of the nomogram by X title, and the more scores, the poorer of prognosis with patients, this indicated the value of the scores of nomogram (Fig. 4 and Fig. 5).

4. Discussion
Glioma is a collective term for malignant tumors derived from glial cells and neuronal cells in the nervous system. Primary tumors of the central nervous system, known as gliomas, occur in 18.7 out of every 100,000 people in the United States. There are 7 cases per 100,000 people in the world, and more than half of the patients are glioblastoma, and their five-year survival period is less than 5%\(^{10–12}\). Genetic diseases (type I neurofibromatosis, tuberculous sclerosis), electromagnetic radiation, etc. may be related to the generation of gliomas\(^{13, 14}\). The symptoms caused by glioma are mainly related to the size, location and growth rate of the tumor. Typical clinical symptoms include headache, nausea, vomiting, blurred vision etc. may be accompanied by symptoms such as decreased brain function, memory loss, personality changes, visual impairment, and urinary incontinence\(^{15–18}\).

Age, physical status, tumor registration, histological type, and scope of surgical resection are all important prognostic factors affecting the survival of patients with glioma\(^{19, 20}\). Because glioma is highly aggressive\(^{21}\) and located in the skull, it is difficult to predict the patient's CSS due to the complexity of the condition and location. In addition, there is currently no CSS scoring system specifically for the clinical factors of glioma, making it difficult to accurately predict the CSS of glioma patients. Therefore, we developed a CSS prediction system for the clinicopathological factors of glioma.

Our research demonstrated that there are more patients under 60 years old, male, white, well differentiated, tumor size < 3cm, and undergoing surgery. The analysis of the prognostic factors of the disease showed that, except for age, marital status, grade, primary site, surgery, summary stage, other factors (chemotherapy, tumor size, etc.) have no significance in CSS prediction. Based on our research, a prognostic nomogram was developed, which can be used to predict the possibility of survival assessment. In the univariate and multivariate models, the patients who have undergone surgery have achieved good CSS, so it is recommended that patients undergo surgery as much as possible to improve survival.
In short, this is a study that reported the demographics, clinicopathological characteristics, and prognostic factors of gliomas and established a reliable nomogram to predict CSS in patients. This study showed that age, marital status, grade, primary site, surgery, and summary stage are independent prognostic factors affecting CSS in patients with glial pathways. However, this study also had certain limitations. For example, because the SEER database does not fully include unmeasured confounders that contribute to survival bias, such as comorbidities, different treatment options may result.

**Abbreviations**

CSS  cancer-specific survival  
SEER  Surveillance, Epidemiology, and End Results  
ICD  International Classification of Diseases  
SPSS  Statistical Product and Service Solutions  
CI  confidence interval  
HR  risk ratio  
DCA  Decision curve analysis

**Declarations**

**Ethics approval and consent to participate**

The data comes from the SEER database and belongs to the OA database, so there is no need for ethics approval and consent to participate.

**Agree to publish**

All authors agree to publish.

**Data availability**

The datasets generated during and/or analysed during the current study are available from the corresponding authors on reasonable request.

**Conflict of interest**

The authors have no conflicts of interest to declare.

**funds**
There is No funds.

**Author's contribution**

Junming Xu wrote the article.

Honglin Li downloads data and plots.

Yuanyuan zou provides article ideas and structure.

Chunjiao Yu modified the article.

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**Figures**
Figure 1

A nomogram for predicting the 1,3,5-year CSS of Glioma
Figure 2

Nomogram model calibration curves

A  Test set

B  Validation set
**Figure 3**

Decision curve analysis for nomogram. The y-axis represents net benefit. The X-axis shows the threshold probability.

![Decision curve analysis](image)

**Figure 4**

The overall survival of the nomogram with different score (A and B).

![Overall survival](image)

**Figure 5**

The overall survival of the nomogram with different score.