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RESEARCH

Postoperative prognostic nomogram for adult grade II/III astrocytoma in the Chinese Han population

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Abstract

Background: Prognostic models of glioma have been the focus of many studies. However, most of them are based on Western populations. Additionally, because of the complexity of healthcare data in China, it is important to select a suitable model based on existing clinical data. This study aimed to develop and independently validate a nomogram for predicting the overall survival (OS) with newly diagnosed grade II/III astrocytoma after surgery.

Methods: Data of 472 patients with astrocytoma (grades II–III) were collected from Qilu Hospital as training cohort while data of 250 participants from Linyi People's Hospital were collected as validation cohort. Cox proportional hazards model was used to construct the nomogram and individually predicted 1-, 3-, and 5-year survival probabilities. Calibration ability, and discrimination ability were analyzed in both training and validation cohort.

Results: Overall survival was negatively associated with histopathology, age, subtotal resection, multiple tumors, lower KPS and midline tumors. Internal validation and external validation showed good discrimination (The C-index for 1-, 3-, and 5-year survival were 0.791, 0.748, 0.733 in internal validation and 0.754, 0.735, 0.730 in external validation, respectively). The calibration curves showed good agreement between the predicted and actual 1-, 3-, and 5-year OS rates.

Conclusion: This is the first nomogram study that integrates common clinicopathological factors to provide an individual probabilistic prognosis prediction for Chinese Han patients with astrocytoma (grades II–III). This model can serve as an easy-to-use tool to advise patients and establish optimized surveillance approaches after surgery.

Keywords: Astrocytoma, Cox proportional hazards models, Survival, Nomograms, Prognosis

Introduction

Glioma is the most common type of brain tumor, comprising approximately three-fourths of malignant primary brain tumors in adults [1]. Diffuse infiltrating astrocytomas are the main type of glioma, including diffuse astrocytoma (WHO grade II) and anaplastic astrocytoma (WHO grade III) [2]. Due to their high invasiveness, complete resection is almost impossible. The prognosis is still poor despite effective systemic chemotherapy and radiotherapy [3], with 50% of diffuse astrocytoma and 30% of anaplastic astrocytoma patients surviving 5 years after diagnosis [4]. Malignant progression to higher WHO grade gliomas, including glioblastoma (GBM), is almost inevitable. Thus, adult diffuse infiltrating astrocytomas are ultimately lethal malignant tumors regardless of WHO classification [5].

Although the 2016 World Health Organization (WHO) classification has incorporated molecular markers, mainly for isocitrate dehydrogenase (IDH), into the new definition of diffuse astrocytoma (grade II/III) [6],

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while oligodendroglioma is defined both by IDH and 1p/19q co-deletion [6, 7], and genetic testing technology is becoming more and more available, the reality is that molecular examination is not a routinely performed procedure in most hospitals in China due to the cost [8–10]. As a result, molecular information could not be available for many patients with astrocytomas (grade II/III). Thus, there is a need for tools that aid in predicting the overall survival of astrocytomas (grade II/III) through easily acquired clinical variables to better fit with modern practice.

Multiple prognostic models have been developed based on a combination of clinical variables among different types of glioma, such as GBM and low-grade gliomas (LGGs). Jacob et al. [11] built a prognostic model for patients ≥ 70 years of age with newly diagnosed GBM based on both pretreatment factors [age and Karnofsky performance status (KPS)] and extent of surgery. Application of this prognostic model to the French cohort resulted in significantly different ($P < 0.001$) median survivals for different risk subgroups. Thierry Gorlia et al. [12] constructed prognostic models in a more homogeneous LGGs European population diagnosed by central pathology review based on pretreatment factors (baseline neurological deficits, time since first symptoms, astrocytic tumor type and diameter of tumor). The performance of the model was 0.67 measured by the Harrell's concordance statistic (C-index). Chul-Kee Park et al. [13] evaluated the hierarchical risk groups for the estimated survival of WHO grade III glioma with the patients from a Korean hospital. The model was based on five prognostic factors, including histological subset, age, performance status, extent of resection, and treatment modality. Survival analysis showed significant differences in mean survival between different risk groups ($P < 0.001$). Additionally, a preoperative scale (tumor involvement of prespecified eloquent/critical brain regions, KPS, and tumor volume) has been used for identifying recurrent GBM patients likely to have poor, intermediate, and good relative outcomes ($P < 0.001$) [14].

To our knowledge, the prognostic model for astrocytoma (grade II/III) is not well established and therefore, need more attention. Attempts have been made to identify efficient prognostic factors in astrocytoma (grade II/III). Various investigations have shown that tumor grading, other clinical variables (age, performance status, etc.) and therapeutic methods have significant effect on prognosis, as does the extent of resection [2, 15, 16]. Other clinical factors, such as seizure [17, 18], longest duration of first presenting symptom [19], smoking [20] and drinking [21], have also been discussed in many papers.

A nomogram is a graphical depiction of a prediction model that can be used as a statistically based tool for assessing the overall probability of a specific outcome for any individual patient [22]. This study hypothesizes that astrocytoma prognosis can be effectively predicted by clinical variables, which can be applied in most hospitals in China.

Materials and methods

Study population

This was a retrospective cohort analysis. The flow chart is shown in Fig. 1. Data of 472 patients were collected from Qilu Hospital as training set while data of 250 patients were collected from Linyi People's Hospital as validation set. Inclusion criteria of the study were as follows: (1) a histopathological diagnosis of newly-diagnosed astrocytoma [23, 24], including WHO grade II astrocytoma and grade III anaplastic astrocytoma according to the 2016 WHO classification [6]; (2) underwent surgery between January 2010 and May 2018 for training set, between December 2010 to September 2017 for validation set, respectively; and (3) age ≥ 18 years (Supplemental Fig. 1).

We restricted our investigation to factors that have been associated with astrocytoma (grade II/III) prognosis in previous studies. In addition, these factors were limited to those that are routinely available or can be easily ascertained from existing data systems. For each patient, the following variables were collected by the HIS system in the training set and validation set: baseline demographics of the patients (age at diagnosis, sex, preoperative KPS, seizure history, smoking status, and drinking status), characteristics of the tumor (histopathological diagnosis, midline tumor, single tumor, the blood supply of tumor, tumor margin and tumor texture), and extent of resection. The extent of resection was assessed by the operating neurosurgeon's judgement based on postoperative MRI. The blood supply of the tumor, tumor margin and tumor texture were assessed by the preoperative MRI. Midline tumors included the corpus callosum, septum pellucidum, ventricular system, conarium, brain stem, thalamus, cerebellar vermis and other cerebral midline structures [25]. Single tumors were in contrast with multiple lesion tumors, which were grouped into two categories: multifocal and multicentric [26]. Single tumors and midline tumors were gathered retrospectively from patient medical records and preoperative imaging. Both of the hospitals are Grade A class 3 hospitals and neurosurgeons and radiologists are well trained and experienced. When selecting input variables for the model, all adjuvant therapies, such as chemotherapy and radiotherapy, were excluded to ensure that any prognostic model generated could be used for all patients at the time of histopathologic diagnosis [11].

The details of the missingness are shown in Supplemental Fig. 2. Missing data were imputed via multiple

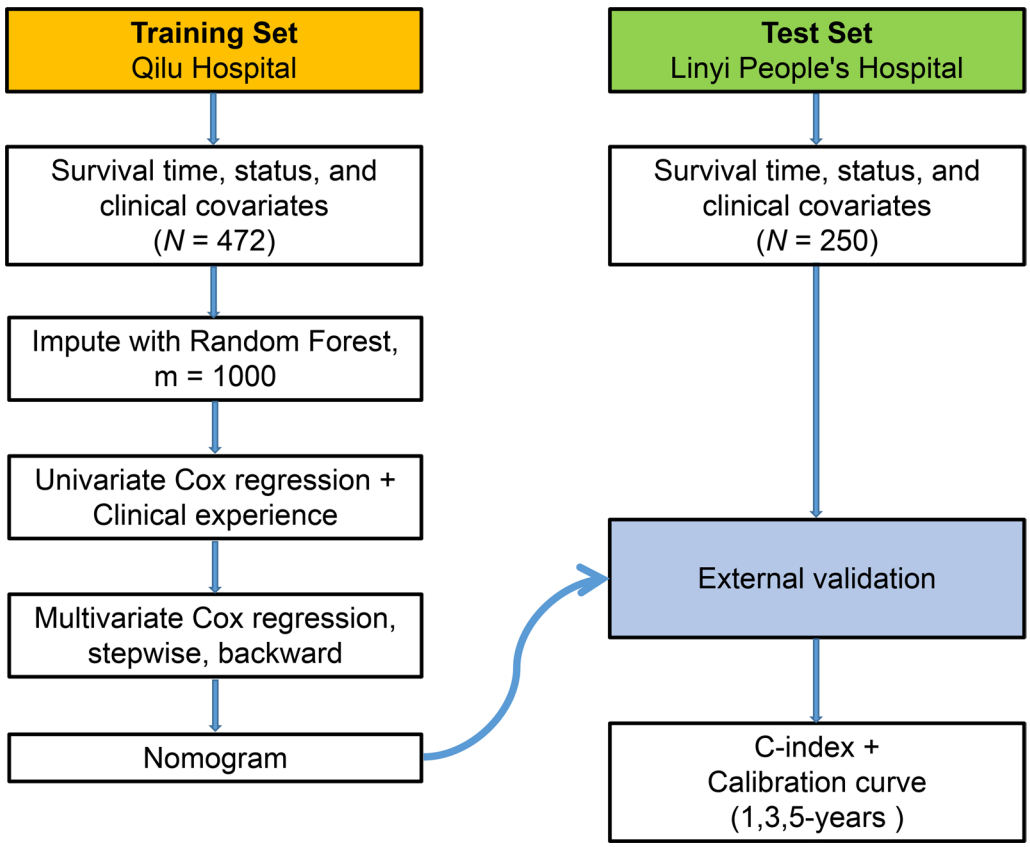

Fig. 1 Flow chart of this study. The clinical nomogram is constructed in training set (N = 472) and validated in test set (N = 250)

imputation using the random forest algorithm with 1000 imputations. All the above 13 variables were included in the model for the imputation.

Follow-up

The primary end point of this study was OS, defined as the interval between the initial diagnosis (date of surgery) and the date of death. Patients still alive were censored. We linked to the database of death registration and medical insurance of Shandong Province by civil ID number, and we also made phone calls to patients and their families for follow-up.

Statistical analysis

Descriptive analyses

Means ± standard deviations (SD) or medians (interquartile ranges, IQRs) were reported for quantitative variables. Frequencies and proportions (N, %) were reported for categorical variables. Quantitative variables were compared using the *t*-test. Categorical variables were compared between groups using the chi-square test. The survival curves for both cohorts were evaluated using the Kaplan–Meier method, and the difference in the survival curves was tested using the log-rank test. The survival curves between the two histopathological grades were evaluated and compared as well.

Model construction

Univariable Cox regression was first performed to test the correlation between overall survival and each clinical variable in the training set. A multivariable Cox regression model was then constructed by including all the variables with a *P* value lower than 0.10 in univariable Cox regression along with other variables that we thought might be related to prognosis but did not demonstrate significance in univariable analysis. The stepwise backward variable selection process was performed in this multivariable Cox regression model based on the maximum Akaike information criterion (AIC) [27]. The number of variables we used was smaller than one tenth of the number of OS events, which is generally thought to have sufficient power in multivariate analyses [28].

Assessment of model performance in the training set

The final Cox regression model was used to individually predicted 1-, 3-, and 5-year survival probabilities.

Internal validation was performed using 1000 bootstrap resamples. The C-index [29] and calibration curve [30] were used to assess the performance of the established model.

External validation

We tested the performance of the 1-, 3-, and 5-year prediction model in the validation set. The C index and calibration curve were used for the external validation.

The prognostic nomogram

A visual prognostic nomogram was derived based on the established Cox regression model for better clinical application. To further validate the prognostic ability, the survival probabilities of all the patients at 12-month after surgery were classified into three subgroups using the tertile values as thresholds. The survival curves of three subgroups were evaluated using the Kaplan–Meier method and compared statistically using the log-rank test.

Sensitivity analysis

To test the robustness of the model, the performance of the nomogram on the raw data without imputation was evaluated and compared with that on the imputed data.

The study was performed in accordance to the transparent reporting of a multivariable prediction model for the individual prognosis or diagnosis (TRIPOD) statement (Supplemental file). All statistical analyses were performed using R v3.5.1 (http://www.rproject.org/). Imputation was performed using the "*mice*" package, stepwise AIC was implemented using the R function "*step*", and the nomogram was built using the "*rms*" package. A 2-sided *P* value of 0.05 was considered statistically significant.

Results

Population characteristics

Table 1 shows the characteristics in the training set and validation set. The median age at diagnosis was 45 years, with the training set slightly younger than the validation set (training set 45 year vs validation set 46 year). The majority of patients were men (training set: 57.84%; validation set: 56.80%). There were significant differences between the two cohorts in terms of KPS score, histopathology diagnosis, tumor resection, blood supply of tumor, tumor margin and tumor texture ($P<0.05$). In addition, there were no significant differences in other clinical characteristics between cohorts, including seizure history, smoking status, and drinking status, etc.

For the entire cohort, the median follow-up period was 36.2 months (interquartile range, 17.7–61.3 months). The median survival was 91.0 months (95% confidence interval [CI], 66.7 to – months, where "–" means the observed time was not reached) for the training set and 66.1 months (95% CI, 41.2 to – months) for the validation set. A significant difference in the median survival time was found between the two cohorts ($P=0.026$) (Fig. 2). The Kaplan–Meier estimates of OS of two tumor grades are shown in Fig. 3.

Model construction

The final Cox regression model included six clinical variables, including age ($P<0.001$, HR = 1.027, 95% CI 1.015–1.040), histopathological diagnosis (anaplastic astrocytoma ($P<0.001$, HR = 2.603, 95% CI 1.915–3.538)), subtotal resection ($P=0.020$, HR = 1.455, 95% CI 1.060–1.997), multiple tumors ($P=0.007$, HR = 1.892, 95% CI 1.194–2.998), midline tumors ($P=0.051$, HR = 1.467, 95% CI 0.999–2.156), and KPS score ($P=0.019$, HR = 0.680, 95% CI 0.493–0.939) (Table 2).

Validation of prognostic model

Supplemental Table 1 shows the discrimination performance of the prognostic model in the training set and validation set. The model yielded good prediction accuracy in the training set (C-index: 0.791, 0.748, and 0.733 at 1, 3, and 5 years) and in the validation set (C-index: 0.754, 0.735, and 0.730 at 1, 3, and 5 years). The calibration curves showed good agreement between the predicted and actual 1-, 3-, and 5-year OS rates in both the training set and validation set (Fig. 4).

Nomogram

On the basis of the final multivariable Cox regression model, we constructed a clinical nomogram that visually depicted the multivariate impact of each variable in the Cox regression model (Fig. 5). An online webserver was built based on the proposed nomogram for convenient clinical use (https://lijiewang.shinyapps.io/DynNomapp/). The survival curves of three subgroups defined according to tertiles of nomogram-predicted survival probabilities were presented in Supplemental Fig. 3 and a significant difference was found in the training set ($P<0.0001$) and testing set ($P<0.0001$).

Sensitivity analysis

The raw data of the clinicopathologic characteristics are shown in Supplemental Table 2. Six variables (age, histopathological diagnosis, resection, single tumor, midline tumor, and KPS score) were included in the Cox model to predict OS. The results of the univariate and multivariate Cox proportional hazards model analyses for OS are presented in Supplemental Table 3. Supplemental Fig. 4 shows the nomogram for predicting the overall survival probabilities of patients at 1, 3 and

Table 1 Descriptive characteristics of the study population

Characteristic	Training set (n = 472)	Validation set (n = 250)	*P* (training set vs validation set)
Age at diagnosis, mean (SD[a]), years	45.41 (12.47)	46.07 (13.07)	0.504
Median (interquartile range)	45.00 (37.00, 54.25)	46.00 (38.00, 56.00)	0.397
Gender, No. (%)			0.850
Women	199 (42.16)	108 (43.20)	
Men	273 (57.84)	142 (56.80)	
KPS[b] score, No. (%)			0.002
≤ 60	124 (26.27)	94 (37.60)	
> 60	348 (73.73)	156 (62.40)	
Seizure history, No. (%)			0.400
No	299 (63.35)	167 (66.80)	
Yes	173 (36.65)	83 (33.20)	
Smoking status, No. (%)			0.110
No	384 (81.36)	190 (76.00)	
Yes	88 (18.64)	60 (24.00)	
Drinking status, No. (%)			0.170
No	386 (81.78)	193 (77.20)	
Yes	86 (18.22)	57 (22.80)	
Histopathology diagnosis, No. (%)			< 0.001
Diffuse astrocytoma, NOS[c]	312 (66.10)	115 (46.00)	
Anaplastic astrocytoma, NOS	160 (33.90)	135 (54.00)	
Midline tumor, No. (%)			0.995
No	398 (84.32)	210 (84.00)	
Yes	74 (15.68)	40 (16.00)	
Resection, No. (%)			< 0.001
Total (gross)	263 (55.72)	171 (69.23)	
Subtotal	209 (44.28)	76 (30.77)	
Single tumor, No. (%)			0.078
Single	437 (92.58)	220 (88.35)	
Multiple	35 (7.42)	29 (11.65)	
Blood supply of tumor, No. (%)			< 0.001
Rich	237 (50.21)	156 (69.64)	
Poor	235 (49.79)	68 (30.36)	
Tumor margin, No. (%)			0.006
Well-defined	61 (12.92)	13 (5.73)	
Obscure	411 (87.08)	214 (94.27)	
Tumor texture, No. (%)			
Hard	233 (49.36)	68 (32.23)	< 0.001
Soft	154 (32.63)	73 (34.60)	
Mixed	85 (18.01)	70 (33.18)	

[a] *SD* standard deviation

[b] *KPS* Karnofsky performance status

[c] *NOS* insufficient information to assign a more specific code, tumors have not been fully tested for the relevant genetic parameters

5 years without imputation. Supplemental Fig. 5 shows the calibration curves for the nomogram. The internal C-index was almost the same as the C-index from imputed data, but the external C-index was slightly lower than the C-index from imputed data, as shown in Supplemental Table 4. This shows that the model is relatively robust.

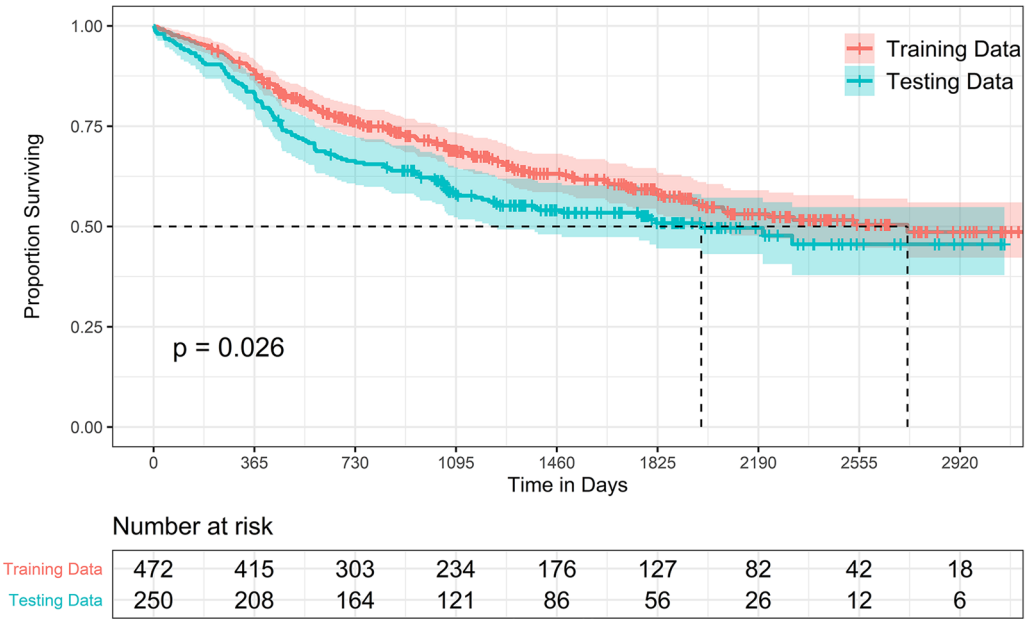

Fig. 2 Kaplan–Meier survival results with 95% CI curves for median survival in days and 95% CI for training data: 2730 (2001, NA) and testing data: 1983 (1237, NA); log-rank test P = 0.026

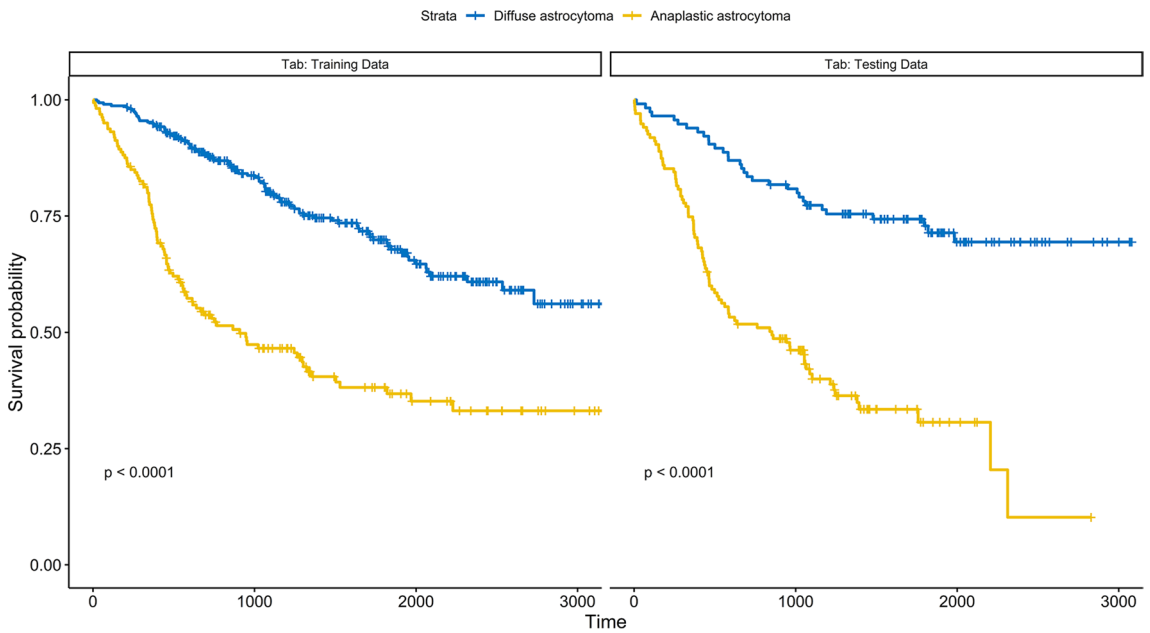

Fig. 3 Kaplan–Meier survival plots stratified by histological grade on overall survival

Discussion

To date, most of the research in this field, including research on anaplastic oligodendroglioma [31] and high grade glioma [32, 33], has been done in Western populations. Only a few studies have investigated the characteristics of glioma in Chinese patients (Asian) [34]. On the one hand, many retrospective studies in the literature were usually conducted on a very small number of patients, which can limit the analyzed accuracy of prognostic factors; on the other hand, the findings of existing analyses based on larger data sets have not been confirmed in subsequent studies. In addition, no externally

Table 2 Cox proportional hazards model showing the association of variables with overall survival

Variable	Univariate analysis			Multivariate analysis		
	Estimate	95% CI	*P*	Estimate	95% CI	*P*
Age at diagnosis (continuous)	1.039	1.026–1.052	< 0.001	1.027	1.015–1.040	< 0.001
Histopathology diagnosis						
Diffuse astrocytoma, NOS[a]	Reference			Reference		
Anaplastic astrocytoma, NOS	2.982	2.223–4.000	< 0.001	2.603	1.915–3.538	< 0.001
Resection						
Total (gross)	Reference			Reference		
Subtotal	1.684	1.255–2.259	0.001	1.455	1.060–1.997	0.020
Single tumor						
Single	Reference			Reference		
Multiple	2.769	1.768–4.337	< 0.001	1.892	1.194–2.998	0.007
Midline tumor						
No	Reference			Reference		
Yes	1.811	1.266–2.591	0.001	1.467	0.999–2.156	0.051
KPS[b] score						
≤ 60	Reference			Reference		
> 60	0.505	0.372–0.685	< 0.001	0.680	0.493–0.939	0.019
Gender						
Women	Reference					
Men	1.381	1.020–1.871	0.037			
Seizure history						
No	Reference					
Yes	0.602	0.436–0.833	0.002			
Blood supply of tumor						
Rich	Reference					
Poor	0.632	0.470–0.850	0.002			
Smoking status						
No	Reference					
Yes	1.166	0.802–1.694	0.421			
Drinking status						
No	Reference					
Yes	1.225	0.839–1.789	0.293			
Tumor margin						
Well-defined	Reference					
Obscure	0.887	0.589–1.336	0.567			
Tumor texture						
Hard	Reference					
Soft	1.201	0.868–1.664	0.269			
Mixed	1.046	0.696–1.571	0.830			

[a] *NOS* insufficient information to assign a more specific code, tumors have not been fully tested for the relevant genetic parameters

[b] *KPS* Karnofsky performance status

validated nomogram has been reported to date because of the rarity of the disease and the difficulty in collecting a sufficient number of patients.

To our knowledge, no such prediction model exists for astrocytoma (grade II/III). Our goal was to obtain a prognostic model suitable for adult Chinese patients with diffuse astrocytoma (grade II/III). We developed a Cox model-based nomogram using data from a large cohort of patients with astrocytic glioma in Qilu Hospital for assessing individual survival probabilities (1-, 3-, and 5-year survival). We validated this model in a large, external, independent dataset. Our model has moderate

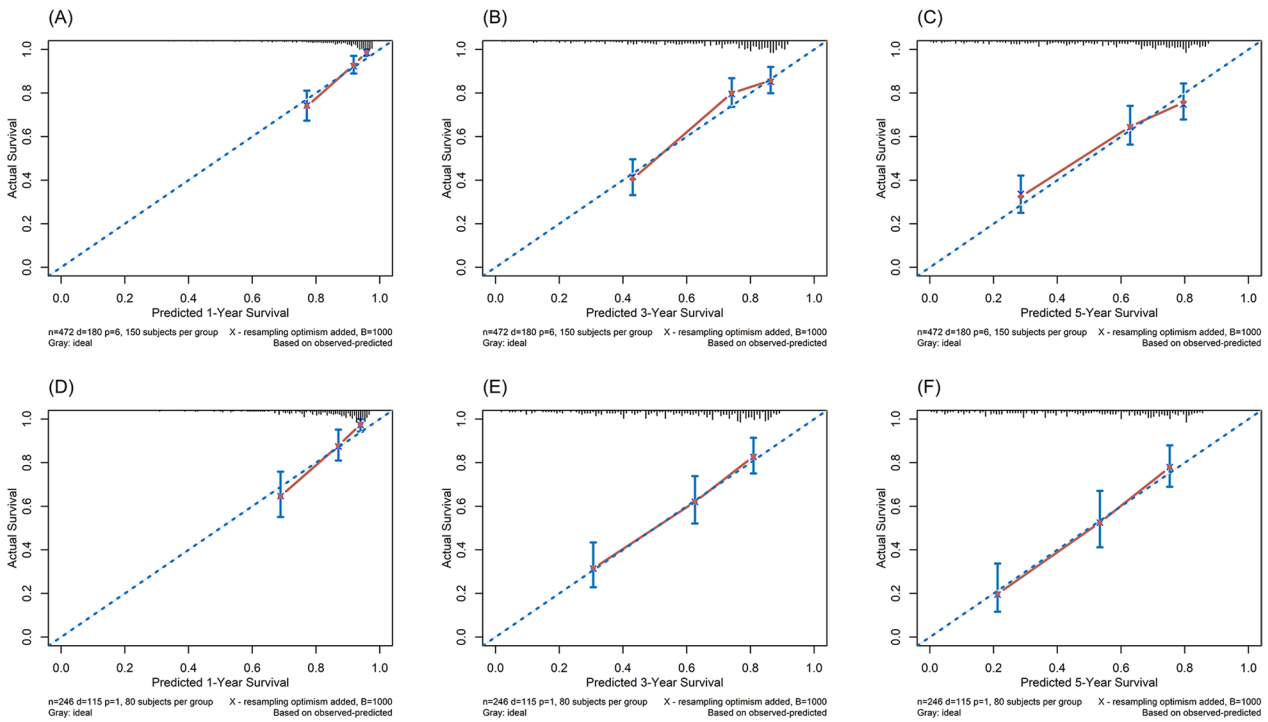

Fig. 4 **A**–**F** Calibration curves for predicting patient survival in the training data at 1 year (**A**), 3 year (**B**), and 5 year (**C**) and for independent validation data at 1 year (**D**), 3 year (**E**), and 5 year (**F**)

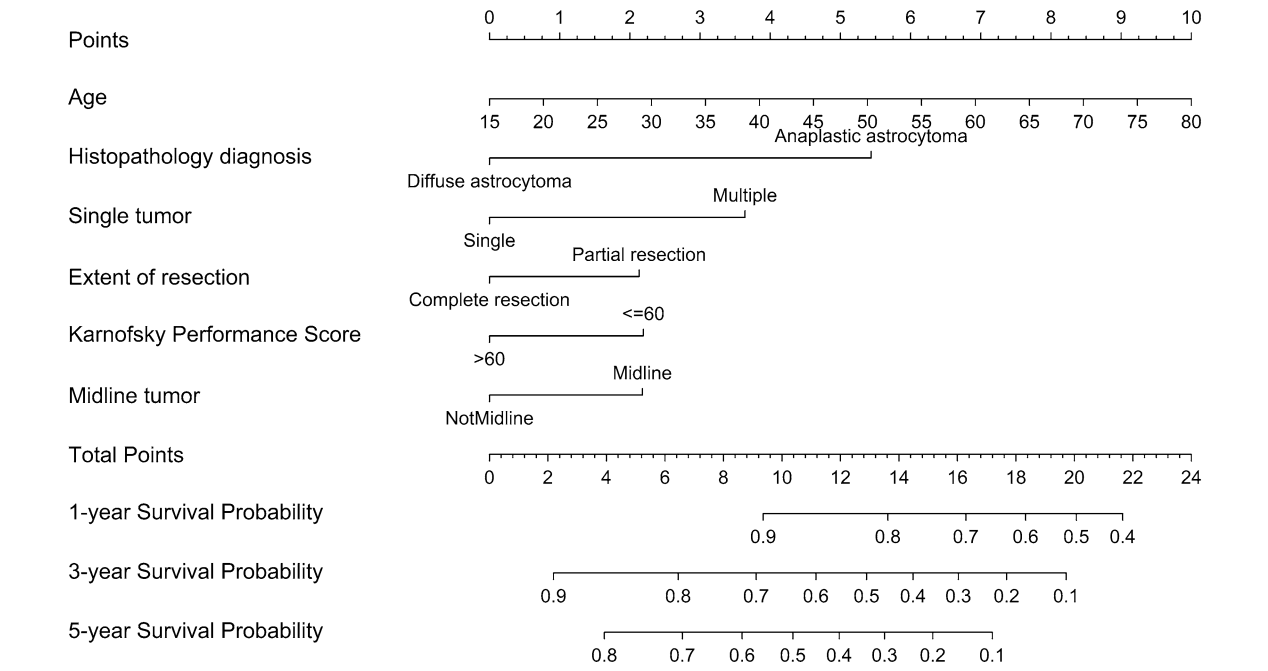

Fig. 5 Nomogram for patients with astrocytic glioma predicting the probability of overall survival at 1-, 3- and 5 years

discrimination, which was indicated by the C-index value of over 0.7 in both the training and testing datasets.

After fitting the univariate and multivariate Cox models in the training dataset, WHO grading, greater age at diagnosis, lower KPS scores, subtotal resection, multiple tumors, and midline tumors were the six most powerful prognostic variables and had a significant impact on survival in our study. Certainly, age is a critical prognostic factor that has been successfully applied to the prognosis prediction of glioma, including but not limited to WHO grade II [35], anaplastic gliomas [13, 36], and glioblastoma [22]. The KPS score was also proved to be an important factor in glioma prognostics based on a recent study by Gittleman et al. [37]. The survival rate of patients decreases as the KPS score decreases [38]. When compared with total resection, subtotal resection exerts a negative effect on patient survival and can thus serve as a strong indicator [39, 40]. Multiple and midline tumors have been demonstrated to be harmful to survival due to the increased difficulty in surgery and recovery [35, 39]. In a recent study [37], it was shown that sex was not a significant factor for glioma prognosis (WHO II and III) with a *P*-value of 0.445, which is consistent with our finding.

IDH mutation appears early in glioma formation and has an important impact on patient survival [41]. The IDH mutation status was primarily tested through immunohistochemistry in routine glioma management. Only a limited number of patients, to be more specific, 132 patients in the training set and 67 patients in the testing set, had the IDH status tested by immunohistochemistry method. For immunohistochemistry negative case, DNA sequencing needs to be done for determining the mutation status of IDH. In common clinical practice in China, it is, obviously, not ethical or economical to have the molecular examination on every patient. On the other hand, the IDH mutation information was absent because of the retrospective nature of the current study where most patients were collected before 2016, earlier than the time when the 2016 WHO classification was released.

There are several limitations in this study. Similar to other studies, the series generated in this study is retrospective and can therefore potentially be subjected to bias and variation. Our follow-up was not long enough to obtain the end point for all patients. Consequently, for grade II astrocytoma, we did not reach the exact median survival time. Further efforts on patient follow-up are encouraged to improve our model. Chemotherapy and radiotherapy can be important factors related to the overall survival. In the original data from the two hospitals in this study, some patients only finish part of the chemotherapy or radiotherapy treatment process after surgery (including total resection) due to the high costs. This makes it quite difficult to draw a solid conclusion in this case of not enough data. Besides, the major aim of our study is to provide the prognosis after surgery. This is quite important since it could help patients decide whether to accept the surgery or not by providing the predictions of the overall survival. Notably, other information, such as the tumor size, preoperative presence of neurological signs and symptoms of brain tissue destruction, postoperative disappearance of original symptoms and signs or occurrence of new symptoms and signs are also important factors related to the disease. We will keep expanding our dataset so as to include more additional relevant information in future studies. What's more, the lack of 1p/19q co-deletion information may yield latent bias. A very small subset of astrocytomas (grade II/III) diagnostically by histology may have 1p/19q codeletion and molecularly classified as oligodendroglioma [42]. We will try to collect more data of patients who have these factors prospectively and make a further analysis in future. The inclusion of such factors in our model might may help to improve the predictive precision.

Despite these limitations, to the best of our knowledge, this study is the first to develop a nomogram for predicting the overall survival of astrocytoma patients based on a large-scale sample of the patient population. Because of the complexity of healthcare data, it is important to select a suitable modeling method based on existing clinical data. This nomogram offered a reliable and accurate prediction. We expect our proposed model for astrocytoma can serve as the basis for expanding more additional demographic, clinical, and molecular prognostic markers, yielding more precise, individualized survival estimates and adopted in the patient care setting as well as the clinical trial setting.

In summary, we have developed a nomogram that accurately predicts the 1-, 3-, and 5-year survival probabilities of Chinese Han patients with newly diagnosed astrocytoma (grade II/III). This model can serve as an easy-to-use tool to predict survival and to help with developing individualized management and therapies for astrocytoma patients.

Abbreviations

OS: Overall survival; GBM: Glioblastoma; WHO: World Health Organization; IDH: Isocitrate dehydrogenase; KPS: Karnofsky performance status; LGGs: Low-grade gliomas; SD: Standard deviations; IQRs: Interquartile ranges; AIC: Akaike information criterion; C-index: Concordance index; CI: Confidence interval; MMSE: Mini-Mental State Examination.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s13755-023-00223-0.

Below is the link to the electronic supplementary material.Supplementary file1 (DOCX 3890 KB)

Author contributions
LW, JW, GL, FY and FX contributed to the study conception and design. LW, JW, JZ, HX, LD, FC, XH, ZL, and LY performed the material preparation and data collection. LW, JW, JZ, HX, and LD performed the data analysis and wrote the manuscript. JZ, HX, XZ contributed to the interpretation. QT, YX, YZ, XJ, GL, FY, and FX revised the article critically for important intellectual content. All authors discussed the results and commented on the manuscript. All authors read and approved the final manuscript.

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Declarations

Competing interests
The authors made no disclosures. Author Yeping Xu was employed by the company Synthesis Electronic Technology Co., Ltd. Jinan, China. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical approval and consent to participate
The protocol of this study was approved by the Public Health Ethics Committee of Shandong University (Approval No. LL20200701). The requirement for informed consent was waived because of the retrospective nature of the study. The analysis used anonymous clinical data.

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