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Prognostic Utility of Albumin-to-gamma-Glutamyltransferase Ratio in Patients with High-Grade Glioma and the Development of a Nomogram for Overall Survival

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ABSTRACT

AIM: To assess the prognostic utility of the albumin-to-gamma-glutamyltransferase ratio (AGR) in patients with high-grade glioma (World Health Organization [WHO] grade III and IV) and to develop a predictive nomogram.

MATERIAL and METHODS: Data from 185 patients diagnosed with high-grade gliomas, who underwent surgical treatment between March 2013 and December 2022, were retrospectively analysed. Patients were randomly divided into training and validation cohorts. The nomogram was developed using multivariate Cox regression analysis according to selected risk factors using least absolute shrinkage and selection operator (i.e., "LASSO") regression. The area under the receiver operating characteristic curve, calibration curve, and C-index were used to assess the performance of the prediction model.

RESULTS: This study included data from 185 patients; six independent risk factors were identified and used to generate a prognostic nomogram: WHO grade, body mass index (BMI), smoking, platelet (PLT) count, fibrinogen (FIB) level, and AGR. The nomogram demonstrated considerable prognostic consistency and discrimination. The prognostic utility of AGR was identified in patients with glioma (hazard ratio 0.7876 [95% confidence interval 0.6471–0.9585]; p=0.0172).

CONCLUSION: AGR was a potential risk factor for predicting overall survival in patients with glioma after surgery. The nomogram integrated WHO grade, BMI, smoking status, PLT count, and FIB level. AGR provided clinical guidance for surgeons to predict survival rates in patients with glioma.

KEYWORDS: AGR, Glioma, Nomogram, Overall survival

ABBREVIATIONS: ALB: Albumin, **AUC:** Area under ROC curve, **AGR:** Albumin-to-gamma-glutamyltransferase ratio, **BMI:** Body mass index, **C-index:** Harrell's concordance index; **FIB:** Fibrinogen, **GGT:** Gamma-glutamyltransferase, **LASSO:** Least absolute shrinkage and selection operator (regression); **OS:** Overall survival, **PLR:** Platelet-to-lymphocyte ratio, **PLT:** Platelet, **ROC:** Receiver operating characteristic, **WBC:** White blood cell

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INTRODUCTION

Glioma, the most prevalent histological type of primary central nervous system cancer, is frequently associated with poor prognosis and short overall survival (OS) (20). Gliomas include oligodendrocytes, astrocytes, or a mix of these two cell types, and can be categorised histologically as high-grade (anaplastic astrocytomas, glioblastomas, and anaplastic oligodendrogliomas) and low-grade (oligodendrogliomas and astrocytomas) gliomas (31). Standard treatments and clinical guidance have been developed, including maximally safe surgical resection, radiation therapy, and treatment with temozolomide (26,43,47). Nevertheless, the median survival rate of patients with glioma remains poor (5,8,17). Thus, early prediction and prompt treatment of gliomas are needed to improve prognosis.

Recent studies have demonstrated that the immune response and inflammatory microenvironment play significant roles in tumour progression, with inflammatory biomarkers and various immune cells exhibiting abnormal accumulation (1,32). Accordingly, several inflammation biomarkers and inflammation-related ratio markers have increasingly been evaluated for their prognostic utility, such as OS and progression-free survival in various cancers, including neutrophil-to-lymphocyte ratio, platelet (PLT)-to-lymphocyte ratio (PLR) (10,38), PLT-to-lymphocyte ratio (PLR) (25,39), fibrinogen (FIB)-to-albumin (ALB) ratio (21,24), and monocyte-to-lymphocyte ratio (36,37). However, potential limitations of the predictive model were identified. Therefore, novel prognostic risk factors for gliomas and other malignancies need to be investigated and developed.

ALB is synthesised by the liver and can be used to assess nutritional status and inflammatory responses (2,4). As a potential risk factor, hypoalbuminaemia has prognostic utility in both acute diseases and various cancers (2,19,29,35). Gamma-glutamyltransferase (GGT), a significant enzyme in glutathione metabolism, is involved in evaluating inflammation status, and provides prognostic utility for multiple cancers (15,18). Jing et al. first demonstrated that the ALB-to-GGT ratio (AGR) could be a significant predictor of prognosis in patients with intrahepatic cholangiocarcinoma (13). Several studies have reported the potential prognostic utility of AGR in patients with gallbladder, hepatocellular, and pancreatic cancers (22,40,44).

The aim of the present study, therefore, was to develop a valid, high-grade, glioma prediction nomogram and provide a useful clinical reference for assessing prognostic utility in patients with high-grade gliomas. We also determined the prognostic utility of the AGR in patients with glioma. In contrast to previous reports, our nomogram provides an easy tool for effectively predicting the prognosis of patients with high-grade gliomas.

MATERIAL and METHODS

Patients

A retrospective analysis was performed using the medical records of Subei Hospital (Jiangsu, China) and the Affiliated Hospital of Yangzhou University from March 2013 to December 2022. Inclusion criteria were as follows: patients who underwent surgery, chemotherapy, and/or radiation therapy; patients diagnosed with glioma through histopathological and morphological analyses; and patients with no malignant tumours other than glioma. Patients with incomplete clinical and follow-up data, those with active inflammatory diseases, and those < 18 years of age were excluded. Data from 185 patients with glioma were ultimately included in this study.

Ethics Statement

This study adhered to the ethical guidelines of the Declaration of Helsinki, and all patients provided written informed consent. This study was also supported by the Medical Ethics Committee of Subei Hospital (2021ky138-1).

Data Collection

Basic information from patients with gliomas was systematically collected. Clinical characteristics included age, sex, body mass index (BMI), smoking, alcohol consumption, tumour diameter, and World Health Organization (WHO) grade. Preoperative haematological parameters included red blood cells, haemoglobin, white blood cells (WBCs), lymphocytes, neutrophils, monocytes, PLT, ALB, globulin, albumin-to-globulin ratio, GGT, and FIB. Blood samples were collected before surgery. The AGR index was defined as the ratio of serum ALB level (g/L) to serum GGT level (U/L).

Follow-up

Postoperative follow-up was performed on all patients every three months in the first two years, and then every six months thereafter. Telephone communication was used to collect follow-up data from patients without a scheduled hospital review. Endpoint OS was defined as the time from surgery to death or the last follow-up.

Statistical Analysis

Statistical analysis was performed using R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria <https://www.R-project.org>). All patients with gliomas were randomly divided into primary and validation cohorts in a ratio of 7:3. Subsequently, using a least absolute shrinkage and selection operator (LASSO) regression model, the optimal features for evaluating OS in patients with glioma were selected. A nomogram was developed using multivariate Cox regression analysis based on the selected risk factors. The area under the receiver operating characteristic (ROC) curve (AUC), calibration curve, and C-index (i.e., Harrell's concordance index) were used to evaluate the performance of the prediction model. External validation was performed using the data from the validation cohort.

RESULTS

Patient Characteristics

Clinical data from 230 patients with gliomas, who underwent surgical treatment between March 2013 and December 2022,

were collected (Figure 1), of which 185 were included in this study. The basic characteristics of the training and validation cohorts (ratio, 7:3) are summarised in Table I. The median patient age was 55 years (range, 19–82 years). There were 145 patients with glioblastoma, 32 with anaplastic oligodendroglioma, and eight with anaplastic astrocytoma. The training cohort comprised 130 patients (75 male, 55 female) with gliomas. Seventy-six patients with glioma presented with tumours at multiple locations. Other tumour locations were distributed as follows: occipital lobe (n=3); cerebellum (n=9); thalamus (n=1); temporal lobe (n=44); frontal lobe (n=47); parietal lobe (n=1); and lateral ventricle (n=4). The median OS in patients with gliomas was 15.5 months.

Independent Risk Factors for OS and the Prognostic Nomogram

Independent risk factors were selected to evaluate the OS of patients with glioma based on 25 potential risk factors using LASSO regression (Figure 2A,B). These risk factors included WHO grade, BMI, smoking, FIB, PLT count, and AGR. Accordingly, a prognostic nomogram based on the Cox regression analysis was developed using these six risk factors (Figure 3).

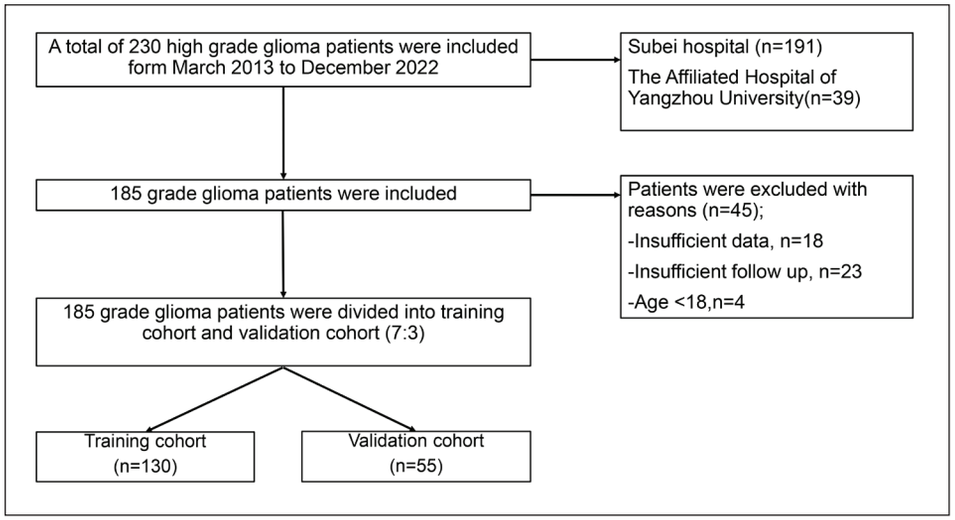

Figure 1: Patient selection.

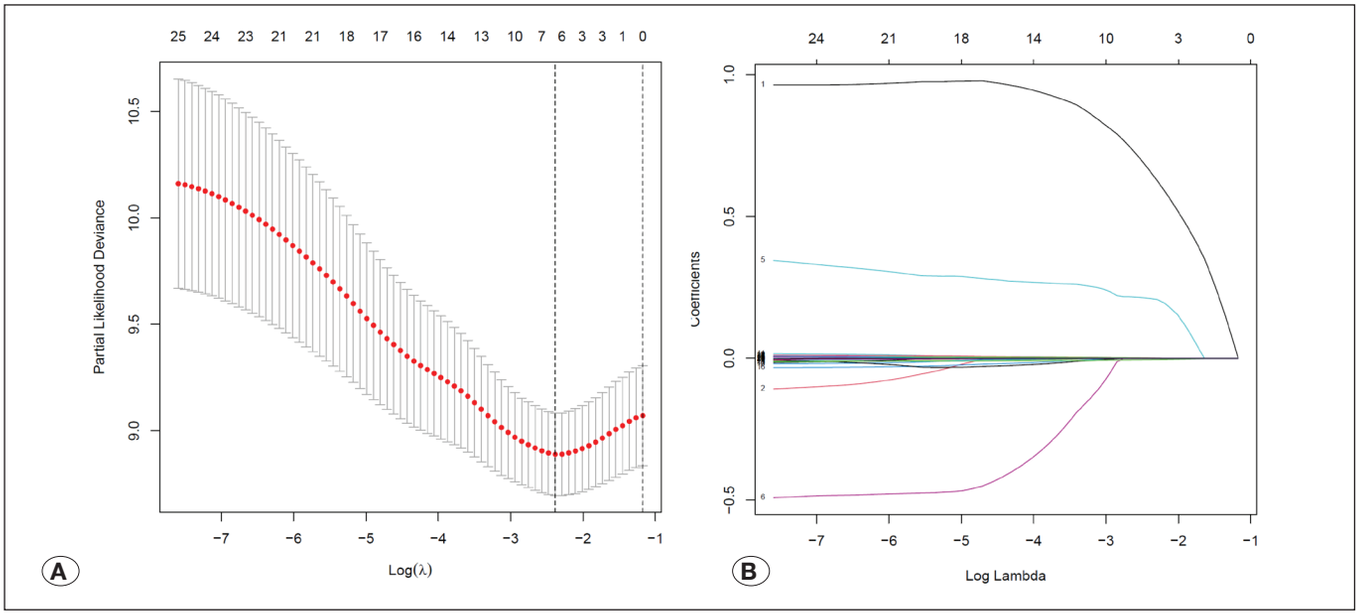

Figure 2: The optimal risk factors selected by the LASSO regression analysis. **A)** The parameters (lambda) selection in the LASSO model used tenfold cross-validation via minimum criteria. The partial likelihood deviance curve was plotted versus log (lambda). Dotted vertical lines were drawn at the optimal values by using the minimum criteria and the 1 SE of the minimum criteria (the 1-SE criteria). **B)** LASSO coefficient profiles of the 25 features. A coefficient profile plot was produced against the log (lambda) sequence. The optimal lambda resulted in six features with nonzero coefficients. Our results showed that six risk factors were selected by LASSO analysis.

Apparent Performance of the Nomogram

The ROC curve demonstrated a strong ability to predict OS in patients with gliomas (Figure 4A). Results demonstrated that AUCs for the nomograms at 1, 2- and 3-years were 0.718, 0.886, and 0.718, respectively. Owing to data limitations, the calibration curve analysis for 1- and 2-year OS revealed good calibration (Figure 5A,B). Discrimination analysis indicated good model discrimination, with a C-index of 0.6620 (95% CI 0.6017–0.7222).

Table I: Basic Characteristics of GBM Patients in Training Cohort and Validation Cohort

	Training cohort n=130, median (interquartile)	Validation cohort n=55, median (interquartile)
Gender, number		
Male	75	24
Female	55	31
Age	55(9)	57(8)
WHO, number		
III	28	12
IV	102	43
BMI	24.65 (1.47)	25.35 (2.80)
Smoking(Yes)	42	14
Alcohol consumption	43	10
Diameter	5(1)	5 (1)
Red blood cell (RBC)	4.42 (0.35)	4.4 (0.31)
Hemoglobin (HGB)	137 (11.25)	135 (12)
White blood cell (WBC)	6.49 (1.14)	6.43 (0.48)
Neutrophils	4.48 (1.145)	4.79 (1.04)
Lymphocyte	1.39 (0.32)	1.44 (0.22)
Monocyte	0.36 (0.09)	0.38 (0.11)
Platelet	180.5 (37.25)	181 (41)
Fibrinogen	2.89 (0.42)	2.96 (0.63)
INR	1.01 (0.05)	1.01 (0.06)
Albumin	43.3 (2.83)	43.4 (4.8)
Globulin	24.6 (2.73)	24.9 (2.5)
Albumin-to-Globulin ratio	1.8 (0.2)	1.7 (0.2)
GGT	20.5 (6.5)	20 (6)
AGR	2.08 (0.86)	2.14 (0.59)
MLR	0.26 (0.08)	0.25 (0.07)
NLR	3.20 (1.11)	3.07 (0.93)
PLR	131.74 (35.76)	119.05 (22.64)
FAR	0.07 (0.01)	0.07 (0.01)

GGT: *Gama-glutamyltransferase,* ***AGR:*** *Albumin-to-gamma-glutamyltransferase ratio,* ***MLR:*** *Monocyte-to-lymphocyte ratio,* ***NLR:*** *Neutrophil-to-lymphocyte ratio,* ***PLR:*** *Platelet-to-lymphocyte ratio,* ***FAR:*** *Fibrinogen-to-albumin ratio.*

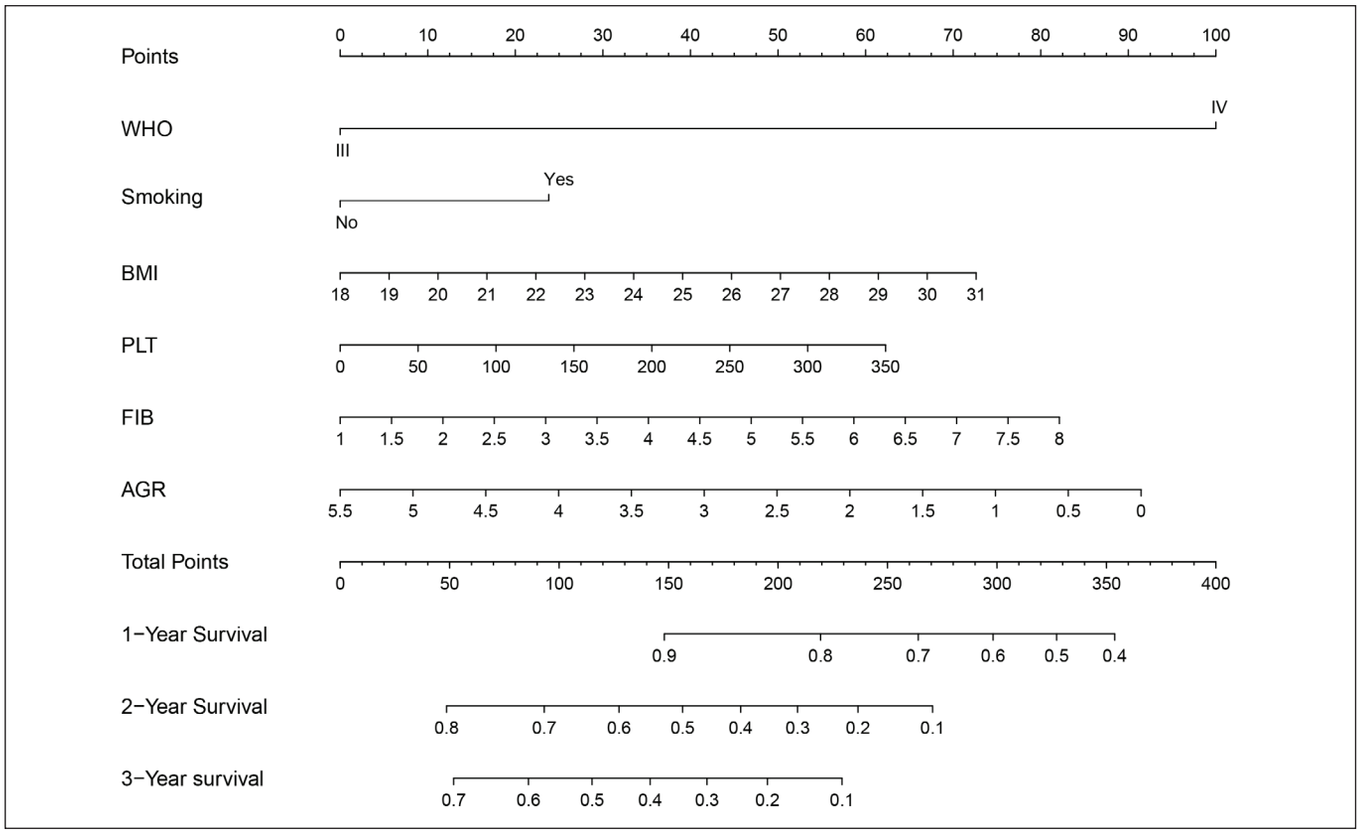

Figure 3: Developed OS nomogram. The nomogram could be applied to predict the OS for glioma patients based on several included risk factors.

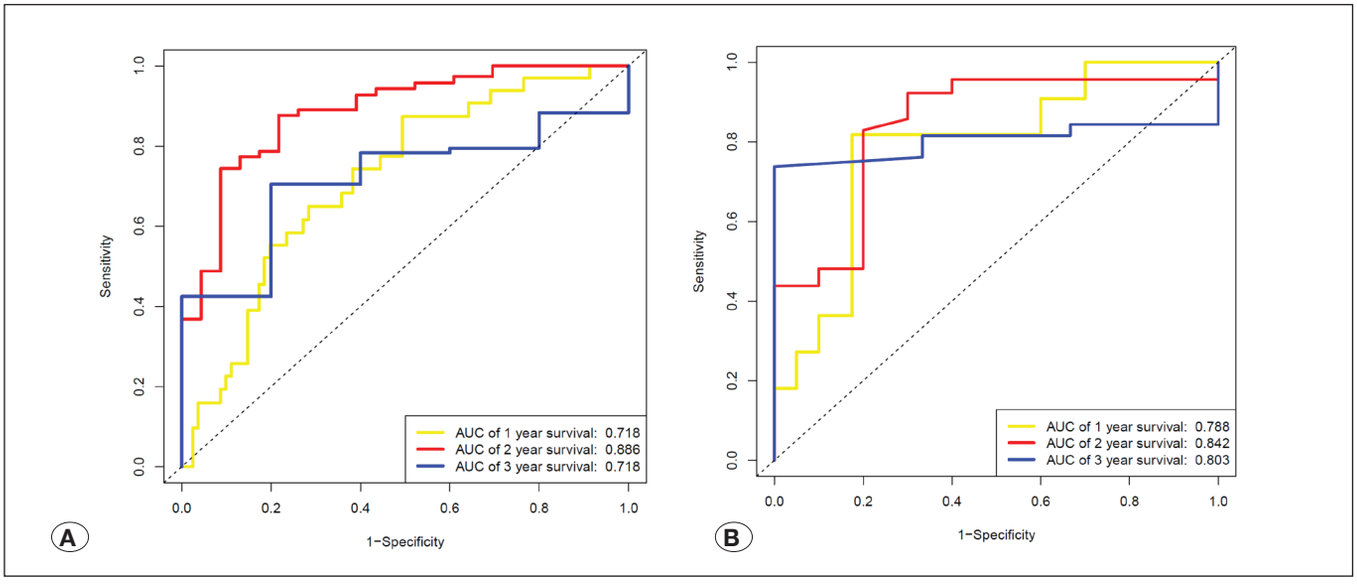

Figure 4: ROC curves of the nomogram and HR value of Cox regression. The results of ROC curves indicated that the nomogram provided a strong ability to predict 1-, 2-, and 3- OS for glioma patients in training cohort **(A)** and validation cohort **(B)**.

External Validation

External validation indicated that the nomogram demonstrated good discrimination and calibration (Figure 5C,D), with a C-index of 0.8301 (95% CI 0.7357–0.9245). In addition, the AUCs for 1-, 2-, and 3-years were 0.788, 0.842, and 0.803, respectively, as illustrated in Figure 4B, reflecting the prognostic utility of the nomogram for OS.

Performance of AGR and Other Independent Risk Factors for OS

The cut-off point of AGR was determined to be 3.092, as calculated using the "survminer" package. For AGR risk, high risk was defined when AGR < 3.092. Kaplan–Meier survival curves indicated that patients with glioma and a high risk for AGR had a short OS (Figure 6). The cut-off values for BMI, PLT, and FIB were 26.61, 115 $\times 10^9$/L, and 3.4, respectively. Additionally, high-risk patients had a BMI > 26.61 kg/m^2, PLT>115 $\times 10^9$/L, a history of smoking, and WHO grade IV.

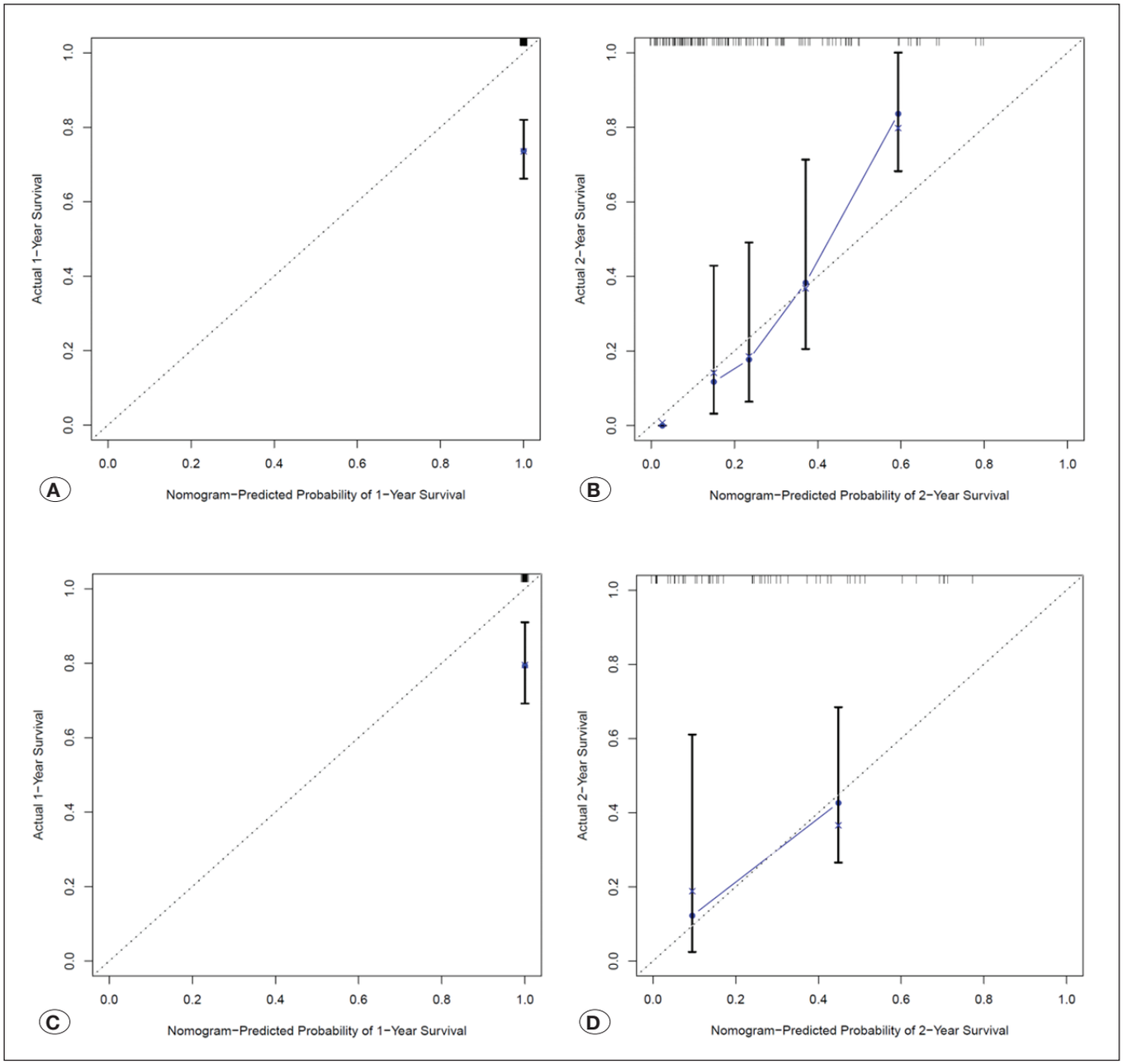

Figure 5: The calibration curve of OS for glioma nomogram. The x-axis represents the predicted probability of survival. The y-axis represents the actually observed survival probability. Calibration curve of the 1- and 2- year OS in the training cohort **(A,B)**. Calibration curve of the 1- and 2- year OS in the validation cohort **(C,D)**.

Risk Stratification Model

A stratification model was used to determine risk in patients with glioma, depending on the prognostic nomogram. The total number of patients ranged from 68.8 to 375.2. Following that, based on total points, patients with glioma were classified as low-risk (total points, 68.8–168.7.7 [n=21]), middle-risk (total points, 168.7–292.4 [n=89]) or high-risk (total points, 292.4–375.2 [n=20]). Results indicated that median OS for patients with glioma in the high- and middle-risk categories was 12.4 and 14.46 months, respectively (p<0.001) (Figure 7).

DISCUSSION

We constructed a prognostic nomogram for OS in patients with glioma incorporating six risk factors: WHO grade, BMI, smoking, FIB, PLT count, and AGR. ROC curve analysis, calibration curve, and C-index results indicated that the nomogram demonstrated good performance.

ALB, mainly synthesised by the liver, is involved in biological functions including sustaining colloid pressure and non-oncotic functions (6). Non-oncotic properties include molecular transport, reduced radical scavenging, capacity to modulate capillary permeability, neutrophil adhesion and activation, haemostatic effects, and regulation of cellular signalling pathways (6,7,9,14,28,30,33). Earlier research has suggested that ALB, as a source of energy, supplies amino acids to cancer cells via lysosomal breakdown. Recently, an interesting study reported that oncogenic Ras-expressing cells regulate micropinocytosis and internalise and degrade extracellular ALB, which may provide cancer cells with intracellular amino acids (3). Additionally, ALB internalised through micropinocyto-

Table II: The Results of Cox Regression Analysis for Six Independent Risk Factors

	β	SE	HR	95%CI	p-value
WHO	1.025403	0.298598	2.7882	1.5530-5.0060	**0.000595**
Smoking	0.271656	0.267656	1.3121	0.7765-2.2172	0.310134
BMI	0.066051	0.050865	1.0683	0.9669-1.1803	0.194096
PLT	0.002893	0.001906	1.0029	0.9992-1.0067	0.129208
FIB	0.087316	0.112021	1.0912	0.8761-1.3592	0.435712
AGR	-0.23878	0.100231	0.787586	0.6471-0.9585	**0.017204**

AGR: *Albumin-to-gamma-glutamyltransferase ratio,* ***BMI:*** *Body mass index,* ***PLT:*** *Platelet,* ***FIB:*** *fibrinogen.*

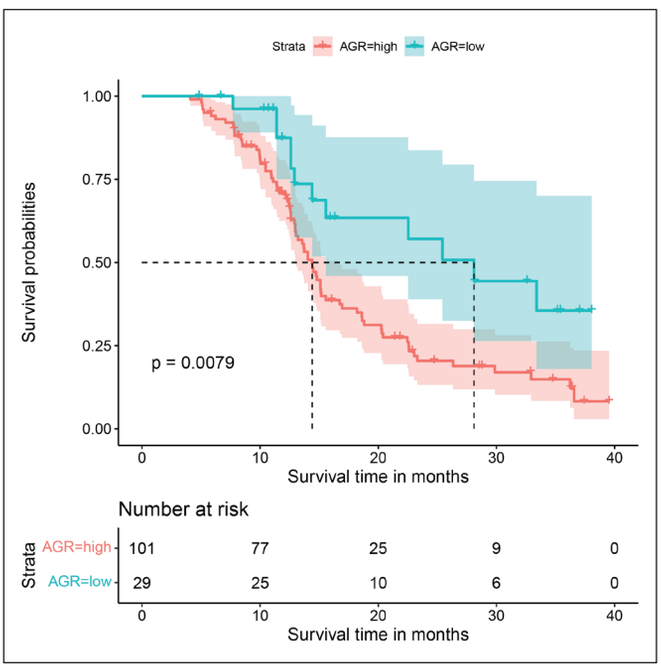

Figure 6: The Kaplan-Meier survival curves for OS based on AGR. Glioma patients were determined as high-risk group with AGR <3.092. The results demonstrated that high risk patients had shorter OS for glioma patients (p=0.0079).

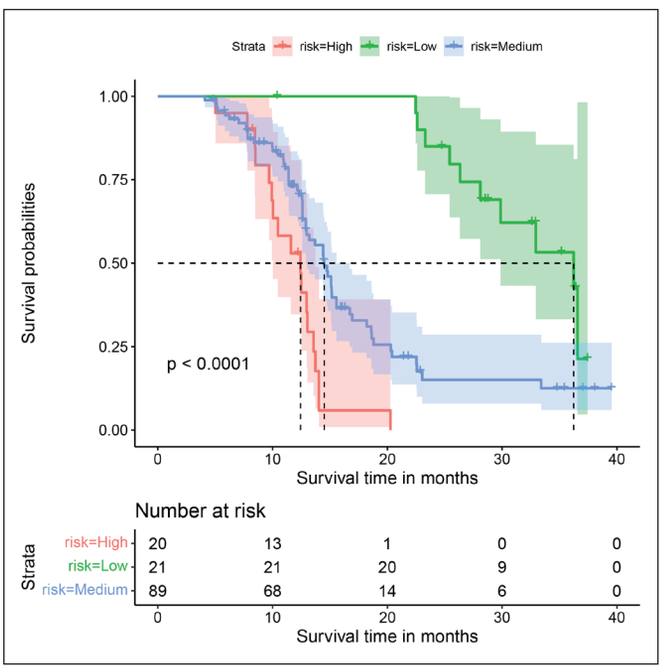

Figure 7: The Kaplan-Meier survival curves for OS based on risk stratification. Compared with low-risk patients and middle risk patients, high-risk patients had a shorter OS for glioma patients based on risk stratification (p<0.0001).

sis maintains the growth of these cells by providing essential amino acids (3). Following glutamine deprivation, cancer cells absorb extracellular ALB as a supplement to provide nutrients for proliferation (3). These results indicate that ALB plays a role in supplementing amino acids required for cancer cell proliferation via macropinocytosis (3).

GGT, an enzyme involved in the gamma-glutamyl cycle, contributes to glutathione metabolism. Serum GGT level has been used as a potential biomarker for evaluating liver function because it is quick, inexpensive, and reliable. In addition, serum GGT levels provide prognostic utility for diverse life-threatening diseases, including metabolic syndrome, diabetes mellitus, cardiovascular disease(s), various liver diseases, and several life-threatening cancers (16,45). Previous studies have demonstrated a link between elevated GGT levels and an increased risk for developing diverse cancers, including oesophageal, laryngeal, stomach, lung, colorectal, bile duct, and female genital organs (27,41,42).

AGR, a combination of ALB and GGT, can be used to evaluate nutritional status and inflammatory response, providing predictive utility for patients with cancer. Previous studies have identified the prognostic significance of AGR in assessing the OS of liver cancers (13,22,40,44). This study identified AGR as an independent risk factor correlated with OS in patients with glioma. Cox regression analysis revealed that patients with glioma and lower AGR levels had shorter OS (hazard ratio 0.5261 [95% CI 0.3916–0.7067]; p<0.0001). Compared with patients with a low AGR, those with a high AGR had longer OS. Based on the AGR cut-off value, patients with glioma were divided into low-risk (AGR ≥ 3.092) and high-risk (AGR < 3.092) groups. The Kaplan–Meier curve suggested that the high-risk group had a shorter OS than the low-risk group.

Other risk factors were also significantly linked to OS in patients with glioma, including WHO grade, BMI, smoking history, FIB level, and PLT count. Similar to previous studies (34,49), our results indicated that WHO grade status is a significant risk factor for predicting OS in patients with glioma. In this study, high-risk patients were classified as WHO grade IV, whereas low-risk patients were classified as WHO grade III. Patients with high-risk glioma have shorter OS. Additionally, BMI was a significant risk factor for assessing the prognosis of patients with glioma. Patients with glioma and a BMI > 26.61 kg/m^2 were considered to be high-risk, accompanied by shorter OS. A previous population-based case-control study reported that patients with a smoking history had an increased risk for death compared with nonsmokers (11). Li et al. demonstrated that patients with glioma who smoked exhibited a higher NF1 mutation level than non-smoking patients, and that patients who smoked had shorter OS (23). FIB and PLT play significant roles in plasma coagulation and are significantly associated with the prognosis of patients with glioma. The prognostic utility of preoperative haematological markers have been evaluated in various cancers. For patients with glioma, a special combination score of FIB and ALB provided a significant prognostic role in evaluating OS (hazard ratio 1.92 [95% CI 1.21–3.05]; p=0.005) (12). In our study, FIB and PLT levels were significantly associated with OS in patients with glioma according to LASSO regression, with the high-risk group exhibiting a shorter OS.

Numerous predictive nomogram models have recently been developed and validated to evaluate their prognostic utility in diverse groups of patients with glioma. However, most of these models focus on prognostic genes based on an online database that reveals that these genes are involved in various functions linked to the immune microenvironment, radiotherapy, ferroptosis, and DNA damage repair (46,48,50). Our model was developed to predict the OS of patients with glioma using several basic characteristics and blood biomarkers. We also performed a risk stratification analysis based on the prognostic nomogram. According to the scores obtained from our nomogram, each patient with glioma was classified as high, middle, or low risk. The results indicated that high-risk patients had short 1-, 2-, and 3-year OS (p<0.0001). Our study provides a simple and effective predictive model for evaluating the prognosis of patients with high-grade gliomas.

However, the present investigation had several limitations. First, it was conducted at only two centres in China; as such, future research should focus on multicentre studies. Second, we included only 185 patients with gliomas, which is a relatively small sample size. We included patients with high grade gliomas (i.e., WHO grades III and IV). The prognostic value of different types of gliomas varies. Finally, various risk factors influence the prognosis of patients with glioma, such as related genes, isocitrate dehydrogenase mutation status, DNA methylation, CDNK2A/B, H3 K27M mutation, H3 G34 mutation, 1p/19 co-deletion, immune cell infiltration (CD4 T cells, B cells, dendritic cells, and macrophages), and radiological features. Numerous prediction models, such as neural networks and other machine learning models, may serve as clinical references for evaluating OS in patients with gliomas.

CONCLUSION

In conclusion, we developed and validated a prognostic nomogram based on six risk factors: WHO grade, BMI, smoking status, PLT count, FIB level, and AGR. Our nomogram may serve as a useful clinical reference for neurosurgeons. Moreover, the AGR could be a potential predictive factor for high-grade gliomas and can be conveniently measured under clinical guidance.

Declarations

Funding: None.

Availability of data and materials: The data used to support the findings of this study are available from the corresponding author upon reasonable request.

Disclosure: The authors declare that there is no conflict of interest.

AUTHORSHIP CONTRIBUTION

Study conception and design: YP, LD, YD
Data collection: EZ
Analysis and interpretation of results: YP, HJ
Draft manuscript preparation: YP
Critical revision of the article: LD, YD
Other (study supervision, fundings, materials, etc...): HJ
All authors (YP, HJ, EZ, LD, YD) reviewed the results and approved the final version of the manuscript.

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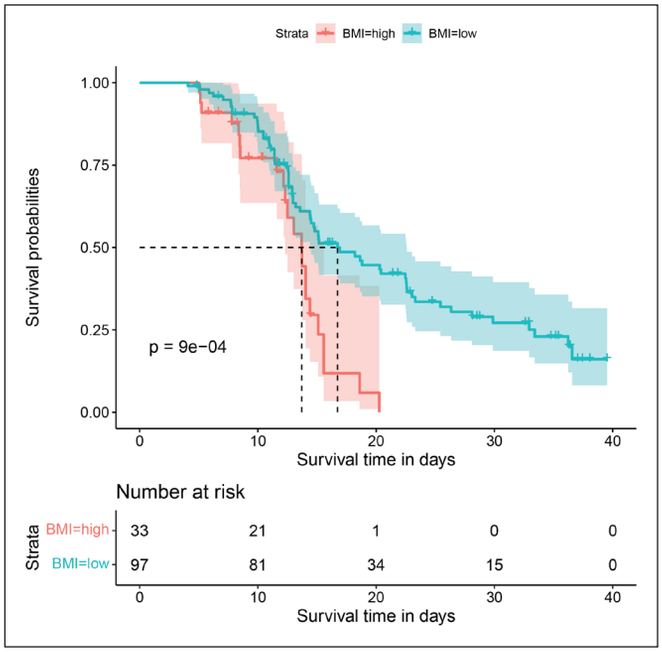
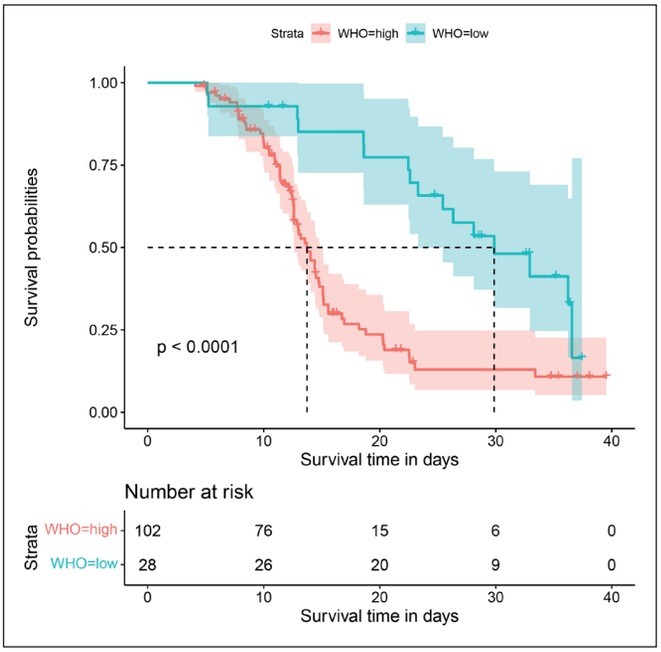
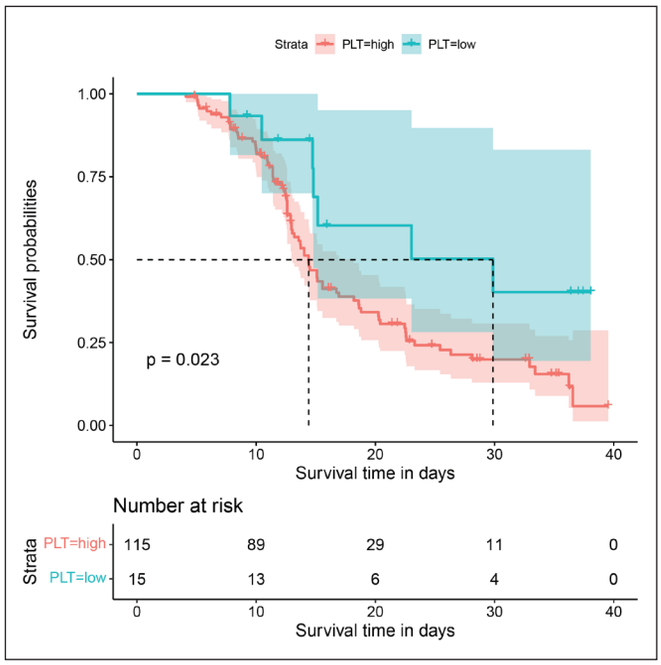


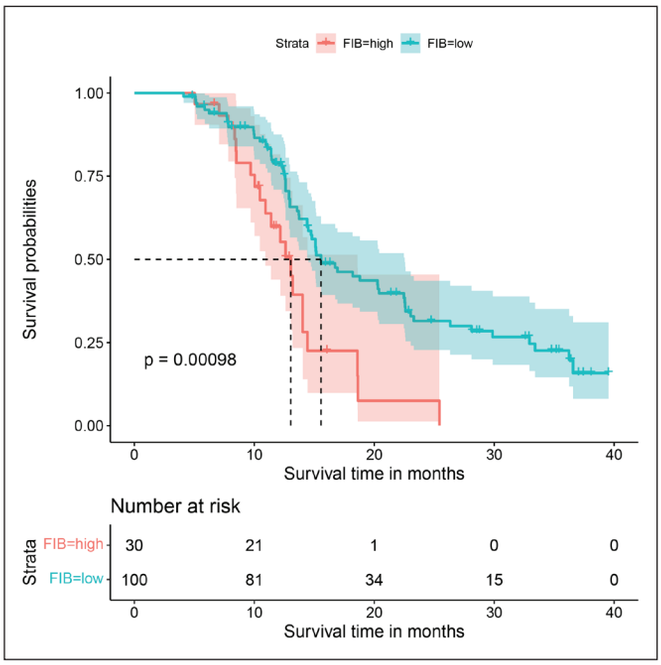
Supplementary Figure 1: The Kaplan-Meier survival curves for OS based on BMI value. The high-risk glioma patients with BMI value >26.61, presented a shorter OS than low-risk patients (p<0.0001).



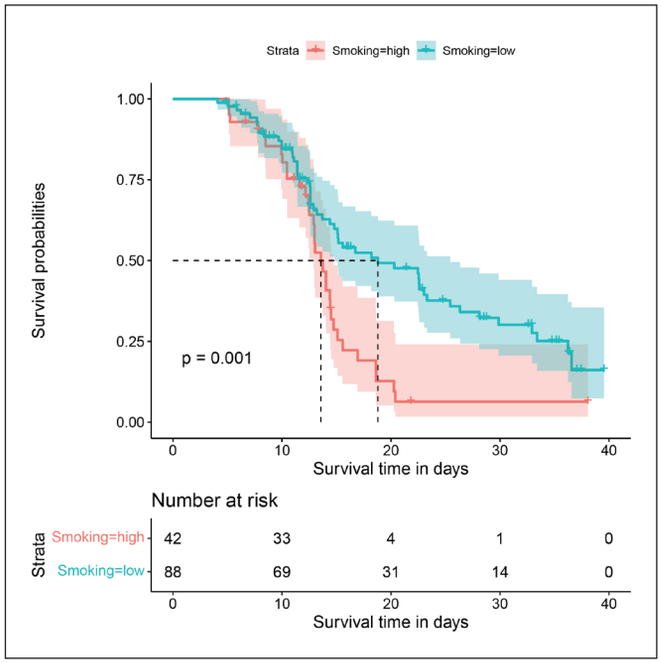
Supplementary Figure 2. The Kaplan-Meier survival curves for OS based on WHO. The high-risk group was defined as glioma patients with WHO IV. The results indicated high-risk group presented a shorter OS than low-risk patients (p<0.0001).



Supplementary Figure 3: The Kaplan-Meier survival curves for OS based on PLT. High-risk group patients with PLT> 115 $\times 10^9$/L, presented a shorter OS (p=0.023).



Supplementary Figure 4: The Kaplan-Meier survival curves for OS based on WHO. The glioma patients were high-risk when FIB >3.4, and high-risk patients had shorter OS (p=0.00098).



Supplementary Figure 5: The Kaplan-Meier survival curves for OS based on smoking history. High-risk group patients with smoking history, presented a shorter OS (p=0.001).