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ORIGINAL RESEARCH

The Prognostic Role and Nomogram Establishment of a Novel Prognostic Score Combining with Fibrinogen and Albumin Levels in Patients with WHO Grade II/III Gliomas

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Purpose: World Health Organization (WHO) Grades II and III gliomas [also known as low grade gliomas (LGGs)] displayed different malignant behaviors and survival outcomes compared to Grade IV gliomas. This study aimed to identify the prognostic predictive value of a novel cumulative prognostic score [combined with fibrinogen and albumin levels (FA score)], establish and validate a point-based nomogram in LGG patients.

Patients and Methods: A total of 91 patients who underwent total glioma resection at Shengjing Hospital of China Medical University between 2011 and 2013 were enrolled to establish a prognostic nomogram. All patients were histologically diagnosed as grades II/III, and never received radiotherapy or chemotherapy before surgery. Data collection included patient characteristics, clinicopathological factors, and preoperative hematology results. The performance of the nomogram was subsequently validated by the concordance index (c-index), calibration curve, and receiver operating characteristic (ROC) curve.

Results: The FA score was negatively associated with the overall survival (OS) of LGG patients ($p < 0.001$). The results of multivariate analysis showed that FA score [$p = 0.006$, HR = 1.92, 95% confidence interval (CI): 1.21–3.05], age ($p = 0.002$, HR = 3.014, 95% CI:1.52–5.97), and white blood count ($p < 0.001$, HR = 4.24, 95% CI: 2.08–8.67) were independent prognostic factors for overall survival (OS). The study established a nomogram to predict OS with a c-index of 0.783 (95% CI, 0.72–0.84).

Conclusion: FA score might be a potential prognostic biomarker for LGG patients, and a reliable point-based nomogram will help clinicians to decide on the best treatment plans.

Keywords: prognostics, fibrinogen, albumin, low-grade gliomas, nomogram

Introduction

Glioma is the most commonly occurring type of malignant primary brain tumor.[1] World Health Organization (WHO) Grades II and III gliomas were recently classified as low-grade gliomas (LGGs).[2,3] LGGs typically appear non-enhancing on magnetic resonance imaging scans, while glioblastomas (GBMs) usually show enhanced signals.[4] It is difficult to distinguish LGGs from GBMs only by histopathology, because they can both show microvascular proliferations, the presence of necrosis, etc.[5,6] LGGs, as opposed to GBMs, display significantly different prognostic outcomes.[7] Histopathology alone is often insufficient to make an accurate prognosis, and so it is necessary to identify prognostic risk factors for LGG patients.

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The histopathological characteristics, age at diagnosis, and performance status are traditional prognostic indicators for gliomas.[8,9] The increasing age and poor performance status (Karnofsky performance score ≤80) are definitive negative prognostic factors.[8] Notably, emerging evidence has indicated that the systemic inflammation level and nutritional status of patients indicated their prognostic values in various solid tumors, including gliomas.[10–13] The cancer-associated inflammation and accumulation of inflammatory cells around cancer cells have been associated with cancer occurrence and progression.[14] Matsuda and co-workers first proposed a novel cumulative prognostic score (FA score) in esophageal cancer, which was combined with fibrinogen and albumin levels. They reported that patients with a high preoperative FA score showed shorter disease-free survival and overall survival.[11] Subsequently, He and co-workers also evaluated the negative prognostic role of high FA scores with overall survival in high grade gliomas (HGGs).[12] However, some issues remained unexplained. For example, only HGG patients were analyzed in previous studies, excluding LGG patients. More importantly, only the FA score was included, and there was no other blood-derived indicator containing a systemic inflammation index.[12] The aim of the present study was therefore to identify the prognostic predictive values of FA scores, which represented the other blood-derived and clinicopathological characteristics in patients with LGGs. To the best of our knowledge, a predictive nomogram for prognoses of LGG patients based on these biomarkers and clinicopathological characteristics has not been previously reported.

Methods and Materials

Study Population

Patients with histologically diagnosed Grade II/III gliomas who underwent curative gross total resection at the Shengjing Hospital of China Medical University between 2011 and 2013 were retrospectively reviewed. The inclusion criteria of patients were as follows: 1) age ≥18 years, 2) Grade II–III gliomas confirmed by histopathology, 3) the surgical procedure involved gross total resection, and 4) the availability of clinicopathological and biochemical data. None of these patients received radiotherapy or chemotherapy before surgery. The study was approved by the Ethics Committee at Shengjing Hospital of China Medical University (2017PS211K). All patients in the study signed informed consent forms. This study was conducted in accordance with the Declaration of Helsinki.

Data Collection

The original clinical data were collected from hospital medical records, including patient age, gender, ECOG PS (Eastern Cooperative Oncology Group performance status), tumor location, maximum tumor diameter and WHO grade. Preoperative blood test indicators included the white blood cell count, hemoglobin, platelet count, neutrophil-to-lymphocyte ratio, platelet-to- lymphocyte ratio, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase, total bilirubin, and direct bilirubin levels. The primary end point of this study was overall survival (OS). OS was counted from the surgery time to the time of death or the last follow-up visit. Patients' deaths were directly related to gliomas.

FA Score and AFR

The fibrinogen cut-off value was defined as 2.5 g/l and the cut-off value of albumin was 38.3 g/l, which were determined by the X-tile program. Patients with elevated fibrinogen and decreased albumin levels were scored 2 points, and only one of the abnormal patients was scored 1 point. None of these abnormalities were scored 0.[11] The patients were divided into three groups based on the best cut-off values of the albumin/fibrinogen ratio (AFR).

Nomogram Development and Validation

For developing a nomogram, the clinicopathological variables that achieved a significance level of $p < 0.2$ using univariate analyses were entered into multivariate analyses for screening as independent risk factors using the Cox regression model. Based on all independent prognostic factors, a nomogram was constructed to allow for a visualized estimate of individual OS probabilities at 1 and 3 years. The nomogram was validated by the bootstrap-corrected Harrell's concordance index (c-index), calibration curves and time-dependent ROC curves.

Statistical Analysis

Laboratory variables were recorded as continuous variables and dichotomized based on the cut-off values determined by the X-tile program (http://www.tissuearray.org/rimmlab).[15,16] A value of $p < 0.05$ was considered significant. The Kaplan-Meier survival method was

used to produce the survival curves. Statistical analyses were performed using SPSS 23.0 software package (SPSS, Chicago, IL, USA) and R software version 3.3.1 (http://www.r-project.org).

Table 1 Relationships Between Patient Demographics and Clinicopathological Characteristics and FA Score with Characteristics

Characteristics	N	Percent/Mean (SD)	FA Score 0 (n=35)	FA Score 1 (n=42)	FA Score 2 (n=14)	P value
Age, years	91	45.42(14.61)	39.74±12.06	46.83±14.50	55.36±15.3	0.002
Gender						0.648
Male	56	61.5%	20(57.1)	26(61.9)	10(71.4)	
Female	35	38.5%	15(42.9)	16(38.1)	4(28.6)	
ECOG PS						0.467
0–1	64	70.3%	27(77.1)	27(64.3)	10(71.4)	
2–3	27	29.7%	8(22.9)	15(35.7)	4(28.6)	
Grade						0.082
II	60	65.9%	28(80.0)	24(57.1)	8(57.1)	
III	31	34.1%	7(20.0)	18(42.9)	6(42.9)	
Location						0.574
Left brain	38	41.8%	13(37.1)	20(47.6)	5(35.7)	
Right brain	53	58.2%	22(62.9)	22(52.4)	9(64.3)	
Max tumor	87	4.822(1.90)	4.62±1.75	4.96±2.03	4.93±1.97	0.735
Adjuvant treatment						0.920
None	35		13	16	6	
Radiotherpy	9		4	4	1	
TMZ	16		8	7	1	
Radiotherpy +TMZ	13		3	7	3	
Unknown	18		7	8	3	
WBC, 10^9/L	91	7.48(3.28)	7.04±2.87	7.62±2.92	8.19±5.00	0.509
HGB, g/L	91	137.01(15.57)	137.7±13.33	136.99±16.94	135.37±15.57	0.896
PLT, 10^9/L	91	212.91(57.32)	205.64±64.52	221.65±47.23	204.86±66.06	0.408
NLR	91	3.41(3.37)	2.79±1.81	3.43±3.16	4.90±5.91	0.140
PLR	91	131.79(54.77)	125.58±61.14	134.16±50.73	140.19±51.74	0.656
TP, g/L	89	67.49(5.58)	68.23±4.66	68.47±5.94	62.82±4.53	0.002
ALB, g/L	91	41.07(4.13)	42.71±2.69	41.52±4.03	35.67±2.95	<0.001
ALT, U/L	86	22.52(20.84)	27.89±28.15	20.05±14.01	14.92±7.29	0.107
AST, U/L	89	17.27(10.29)	19.57±14.64	16.72±6.09	13.07±3.29	0.122
TBIL, umol/L	89	10.11(4.52)	10.96±4.80	10.01±4.38	8.31±3.87	0.176
DBIL, umol/L	89	3.88(2.01)	4.18±1.86	3.65±1.85	3.75±2.78	0.516
Fibrinogen, g/L	91	2.71(0.77)	2.07±0.32	3.06±0.55	3.35±0.96	<0.001
D-dimer, ug/L	87	204.69(298.59)	218.11±409.26	174.59±142.52	258.85±305.62	0.645

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; WBC, white blood cell count; HGB, hemoglobin; PLT, platelet count; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; TP, total protein; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; TMZ, Temozolomide.

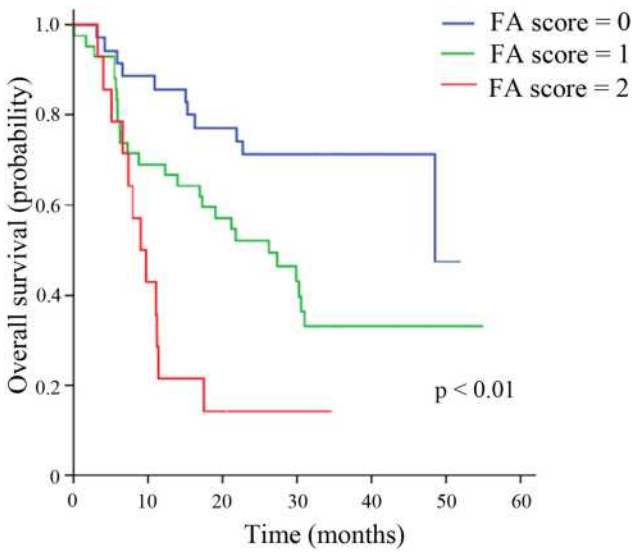

Figure 1 Kaplan-Meier survival curves comparing the three FA score groups.

Results

Patient Characteristics

Between November 2011 and August 2013, 91 patients were included in the final study population (Table 1). Regarding the FA score in patients, 35 (38.5%) were classified with a FA score of 0, 42 (46.2%) were classified with a FA score of 1, and 14 (15.3%) were classified with a FA score of 2. The median age was 45.42 years, and FA scores of the older group had an older mean age (p = 0.002). There were 56 males and 35 females. A total of 60 (65.9%) patients were grade II and 31 (34.1%) patients were grade III. The tumor location of 53 (58.2%) patients was the right brain, and the tumor location of the other patients was the left brain (38, 41.8%). There was no significant difference among the three FA groups in gender (p = 0.648), ECOG PS (p = 0.467), WHO grade (p = 0.082), tumor location (p = 0.574), tumor size (p = 0.735), and adjuvant treatment after surgery (p = 0.920).

The characteristics of total protein (p = 0.002), albumin (p < 0.001), and fibrinogen (p < 0.001) were significantly different among three FA groups. The FA score 1 group had the highest total protein (68.47 ± 5.94 g/L), the FA score 0 group had the highest albumin (42.71 ± 2.69 g/L), and the FA score 2 group had the highest fibrinogen level (3.35 ± 0.96 g/L) (Table 1).

Survival Analysis

On the last follow-up date, 49 (53.8%) patients had died. The median OS of all patients was 29.90 months [95% confidence interval (CI): 21.31–38.49]. The FA score was significantly associated with the OS (p < 0.001) (Figure 1). The patients with the highest FA score (FA score =2) had the worst OS (9.1 months, 95% CI: 5.8–12.3). The median OS for FA scores 0 and 1 were 39.6 months (95% CI: 33.6–45.7) and 26.3 months (95% CI: 14.2–38.3), respectively (Subgroup analysis for grades II and III please see Supplementary Figures 1 and 2).

As shown in Figure 2A, the AFR was positively associated with the OS (p < 0.001). Further comparative analyses showed that the area under curves (AUCs) of FA scores (0.71, 95% CI: 0.60–0.82) was higher than the AFR (0.69; 95% CI: 0.58–0.80) (Figure 2B). We therefore selected the FA score in subsequent survival analyses.

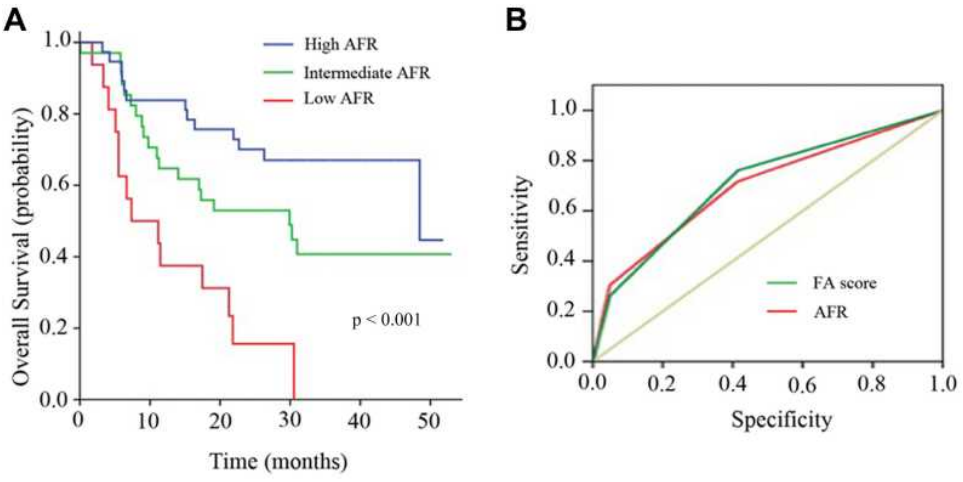

Figure 2 The comparative analyses between FA score and AFR. (**A**). Kaplan-Meier survival curves comparing the three albumin/fibrinogen ratio (AFR) score groups. (**B**). Table 1. Relationships between patient demographics and clinicopathological characteristics and FA score with characteristics.

Table 2 The Result of Univariate Cox Hazards Analysis of Overall Survival

Variables	HR	95% CI	P value
Age <44 ≥44	2.837	1.555–5.178	0.001
Gender Male Female	0.810	0.446–1.473	0.491
ECOG PS 0–1 2–3	2.271	1.281–4.024	0.005
Grade II III	2.948	1.668–5.213	<0.001
Location Left brain Right brain	0.711	0.403–1.256	0.240
Max tumor < 4.8cm ≥ 4.8cm	0.924	0.520–1.639	0.786
Adjuvant treatment	1.103	0.921–1.321	0.288
WBC <8.7*10^9/L ≥8.7*10^9/L	2.390	1.275–4.482	0.007
HGB <132 g/L ≥132 g/L	1.764	0.878–3.545	0.111
PLT <203*10^9/L ≥203*10^9/L	0.665	0.376–1.174	0.159
NLR < 4.1 ≥ 4.1	2.318	1.219–4.410	0.010
PLR <117.4 ≥117.4	1.345	0.767–2.359	0.302
TP <61.6 g/L ≥ 61.6 g/L	0.613	0.274–1.373	0.234
ALB < 38.3 g/L ≥ 38.3 g/L	0.449	0.242–0.834	0.011
ALT < 20 U/L ≥ 20 U/L	1.809	1.004–3.261	0.049
AST < 16 U/L ≥ 16 U/L	0.782	0.430–1.423	0.421
TBIL < 6.8 umol/L ≥ 6.8 umol/L	0.686	0.329–1.427	0.313
DBIL < 2.9 umol/L ≥ 2.9 umol/L	0.648	0.360–1.165	0.147
Fibrinogen <2.5 g/l ≥2.5 g/l	3.155	1.659–6.000	<0.001
D-dimer < 106 ug/L ≥ 106 ug/L	2.264	1.210–4.236	0.011
FA 0 1 2	2.441	1.604–3.715	<0.001

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; WBC, white blood cell count; HGB, hemoglobin; PLT, platelet count; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; TP, total protein; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; FA, fibrinogen and albumin.

Table 3 The Result of Multivariate Cox Hazards Analysis of Overall Survival

Variable	HR	95% CI	P value
Age	3.014	1.522–5.969	0.002
WBC	4.243	2.078–8.666	<0.001
FA	1.916	1.205–3.048	0.006

Abbreviations: WBC, white blood cell count; FA, fibrinogen and albumin.

A Predictive Nomogram for the Prognoses of Patients with Grade II/III Glioma

Univariate and multivariate analyses were used to show that three covariates (FA score, age, and white blood count) had significant correlations with the OS (Tables 2 and 3). Figure 3 shows the predictive nomogram of OS from the multivariate analyses. The c-index was 0.783 (95% CI: 0.72–0.84), indicating good performance of predicting OS for patients with Grade II/III gliomas. The calibration curves for 1- and 3-year survival patients also

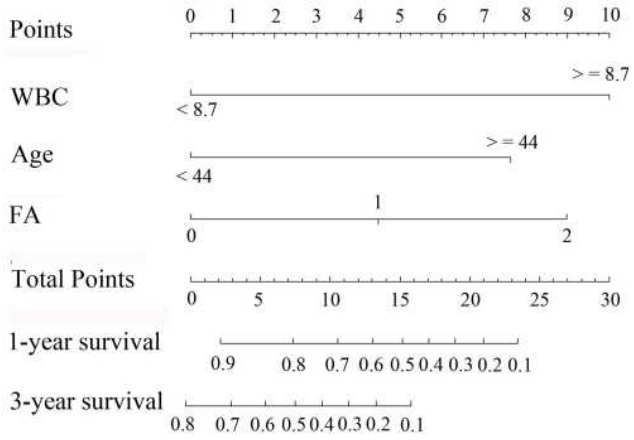

Figure 3 A nomogram predicting 1-year and 3-year overall survival in patients with WHO Grade II/III gliomas.

showed the accurate predictive ability of the nomogram (Figure 4A and B). The time-dependent ROC curve was calculated for the nomogram for every month (Figure 4C).

Discussion

In recent years, an increasing number of studies have focused on the prognosis of GBM, because of its high incidence and prevalence.[17–19] However, LGGs (WHO Grade II/III gliomas) represent important causes of morbidity and mortality in the young adult population.[20] Some past and ongoing clinical trials (NCT02766270, NCT01164189, and NCT03906448) have also focused on LGG patients.[21] Furthermore, it is necessary to identify prognostic factors to optimize treatment for patients with LGGs. In the present study, we showed that the FA score was significantly associated with OS in patients with LGGs, and we developed a nomogram to provide the survival probability of individual patients.

The plasma fibrinogen and albumin level are the most commonly used indicators of coagulation and nutritional status, respectively. Ways to combine fibrinogen and albumin levels, including the AFR and FA score, were reported as prognostic markers in some solid tumors, including HGGs.[11,13,22–26] In the present study, the ROC curve showed that FA scores had a higher sensitivity and specificity than AFR for predicting OS. We showed for the first time a higher FA score was significantly associated with a worse OS, which was an independent prognostic factor in LGGs patients. The exact mechanism for these associations remains unclear. It is well-known that fibrinogen is an acute-phase reactant of systemic inflammation, which includes CRP, leucocytes, ferritin, thrombocytes, and fibrinogen.[27,28] Fibrinogen plays a major role in tumor-related biological behaviors and provides a stable framework for the extracellular matrix of tumors, thus, promoting cancer cell adhesion, migration, and invasion.[29] Albumin is a biomarker of the systemic inflammation response (SIR) and reflects malnutrition and immune ability.[30–32] Some studies have shown that low levels of albumin might be a potential poor prognostic biomarker for gliomas.[33,34] Possible reasons considered to explain this phenomenon are as follows. First, fibrinogen may regulate the SIR by producing tumor-released inflammatory factors such as cytokines interleukin-1, interleukin-6, tumor necrosis factor-α (TNF-α), vascular endothelial growth factor (VEGF), fibroblast growth factor-2, and platelet-derived growth factor.[35–37] IL-6 and TNF-α can suppress synthesis of albumin and VEGF can induce vascular permeability, which lead to a decrease in serum albumin levels.[36,38] Second, malnutrition due to serum albumin levels increases the chance of infection and promotes the development of malignant tumors by accelerating SIR.[39]

Numerous recent studies have provided evidence that some other SIR biomarkers, including the neutrophil-to-

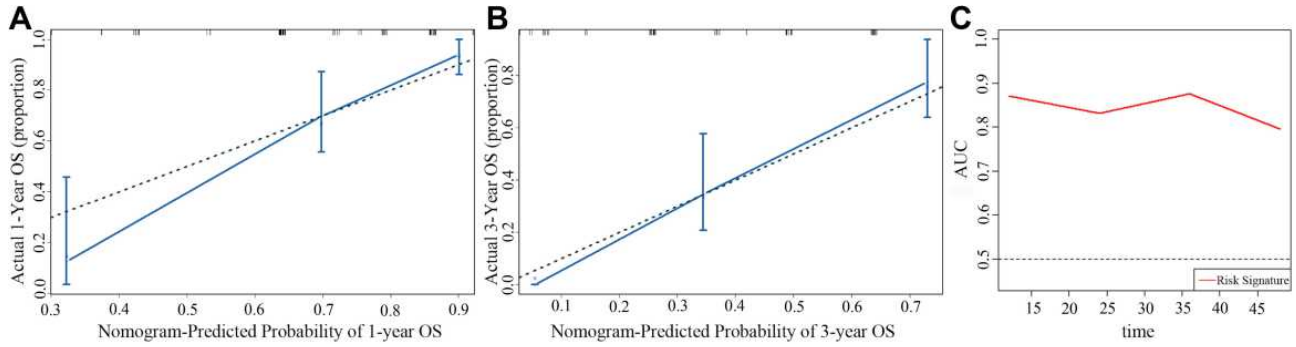

Figure 4 Validation of the nomogram. (**A**). The calibration curve of predicting patient survival percentages at 1 year. (**B**). The calibration curve of predicting patient survival percentages at 3 year. (**C**). The integrated area under the curve was calculated for the nomogram for every month.

lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), are related to the survival of gastric cancer patients.[40–44] In the present study, we also evaluated the prognostic values of PLR and NLR. The results showed that PLR was not an independent predictive index of LGGs, which was consistent with some previous reports in gliomas.[45,46] A recent meta-analysis of 18 studies containing 3261 patients showed that NLR [hazard ratio (HR): 1.38; 95% CI: 1.09–1.74; p = 0.008] was one of the independent indices for predicting the OS of gliomas.[45] In the present study, elevated NLR was statistically significant in univariate analysis but not multivariate analysis. The possible reason was the white blood count was also an independent prognostic factor in LGGs patients in this study. Its large prognostic effect weakened the predictive effect of other leukocyte components.

The nomogram provided a graphic representation of various risk factors and estimated survival probabilities tailored to individual patients.[47,48] The score was obtained based on the result of each variable for each patient by locating the corresponding scale of the variable. The total values were then added, and a vertical line was drawn through the survival scales that provided the probability for a 1- and 3-year OS. This nomogram can effectively promote communication between doctors and patients, to help them select more beneficial treatment options. Our nomogram relied on easily available parameters from clinical-related and hematological characteristics and achieved an AUC value >0.8 for survival prediction. In addition, a good c-index and calibration curve will support the accuracy of the prediction nomogram.

The present study had some limitations. First, this was a retrospective, single center study. A multi-center study with a larger sample size would have been more representative. Second, the nomogram lacked validation cohorts. More patients are needed to establish the internal and external validation cohorts. Third, because the status of tumor recurrence was not accurate and complete, disease free survival data were not analyzed in this study. Fourth, the lack of information on molecular markers (such as IDH status, 1p/19q LOH status, and MGMT promoter methylation status) and postoperative treatment regimens, limited further in-depth analyses.

Conclusions

The FA score was an independent risk factor for OS in LGG patients. A reliable nomogram has great potential application in clinical practice for estimating the mortality risk in treating LGG patients on an individual basis.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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